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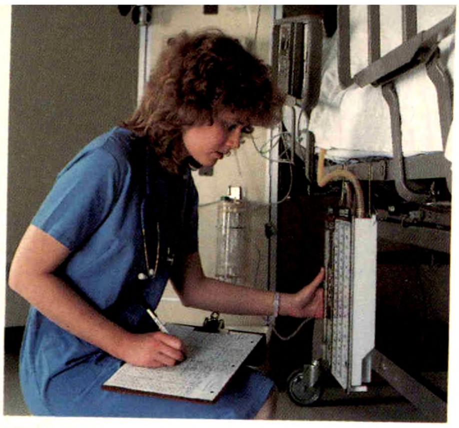

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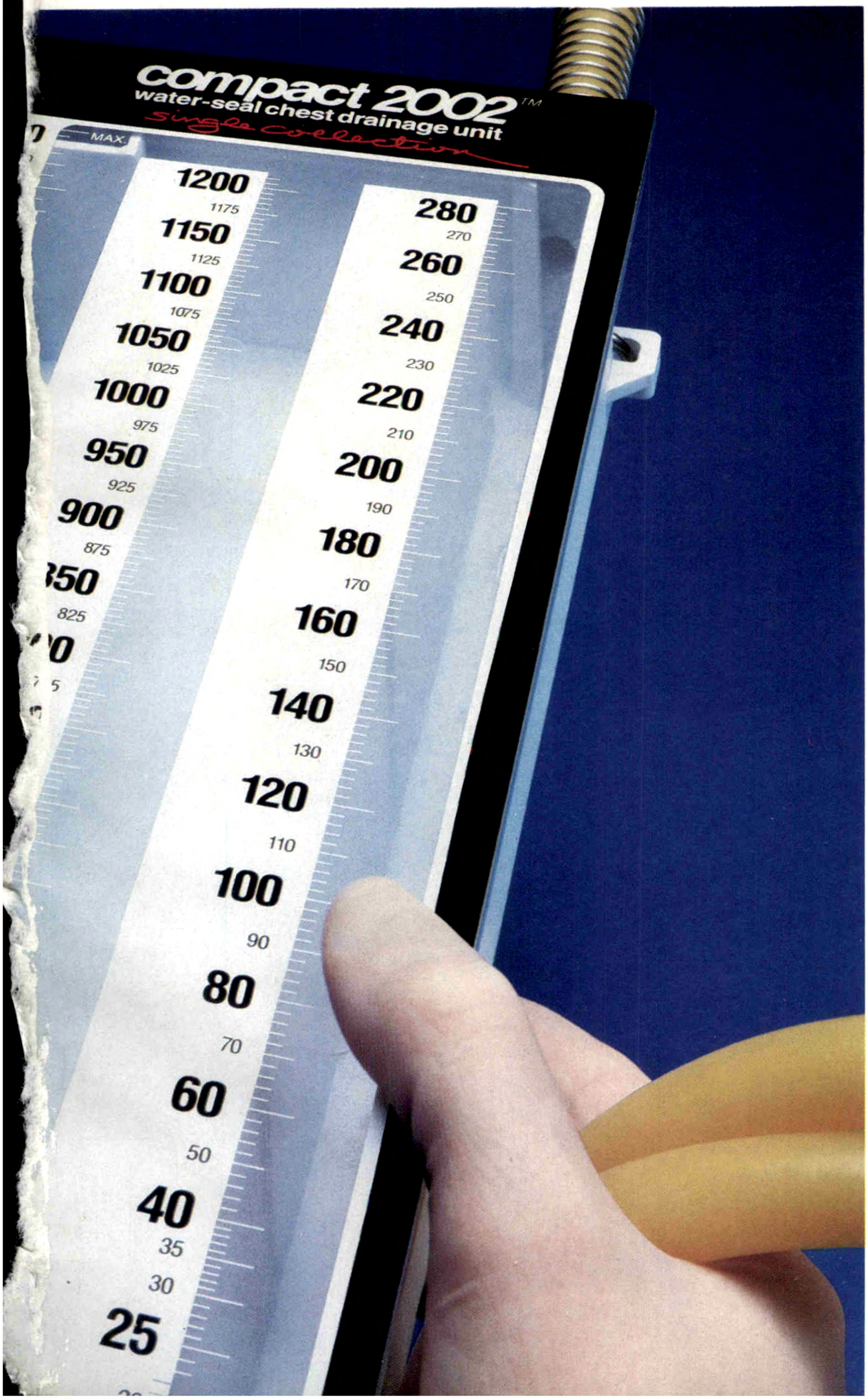

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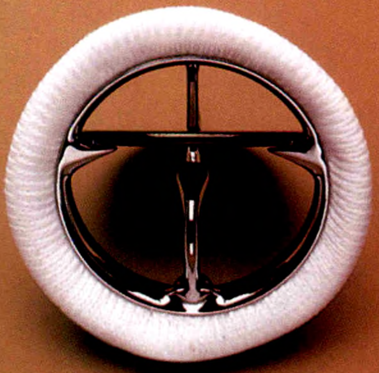

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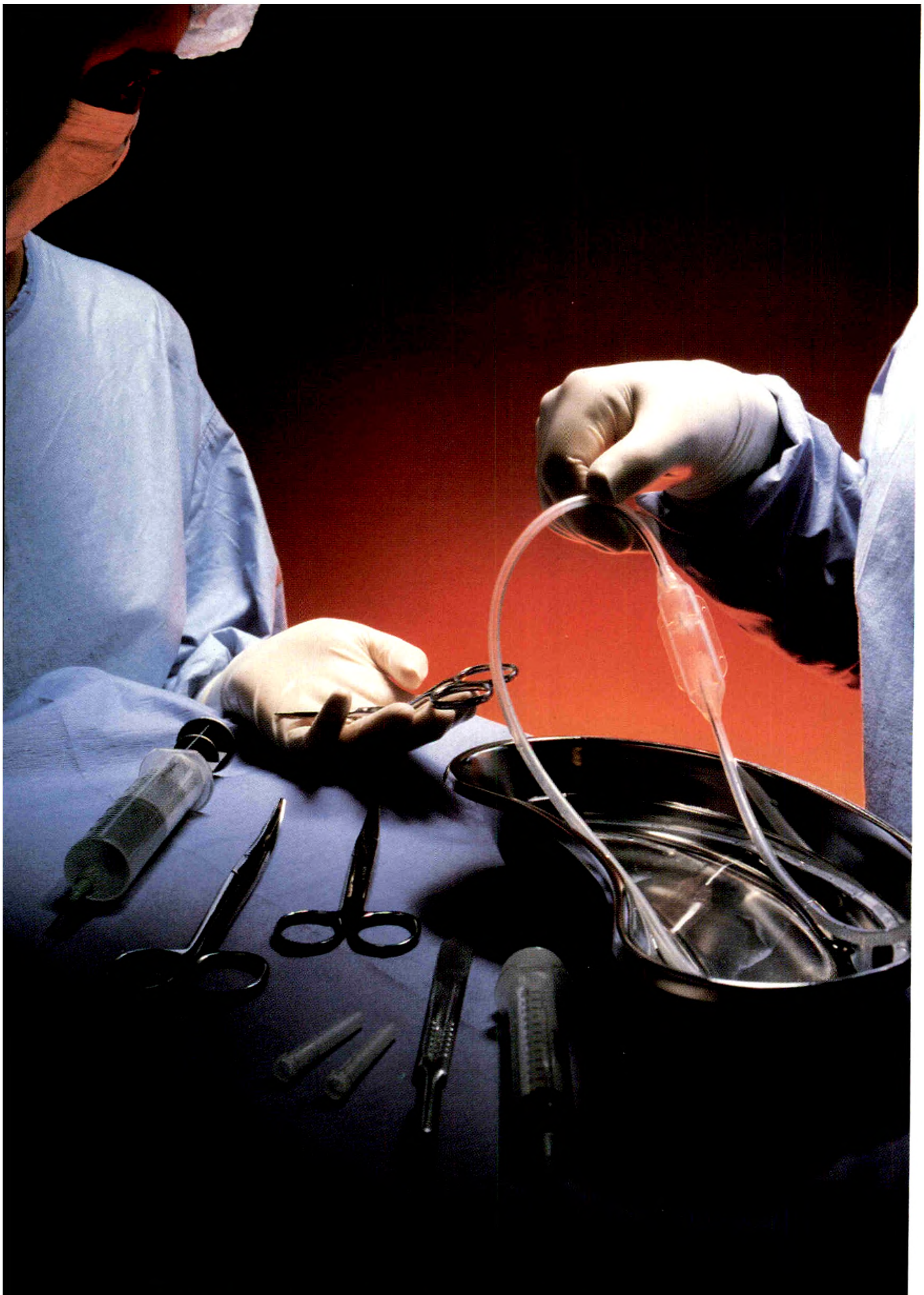

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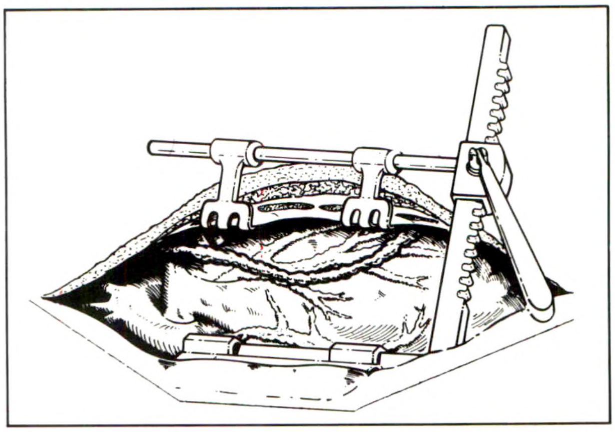

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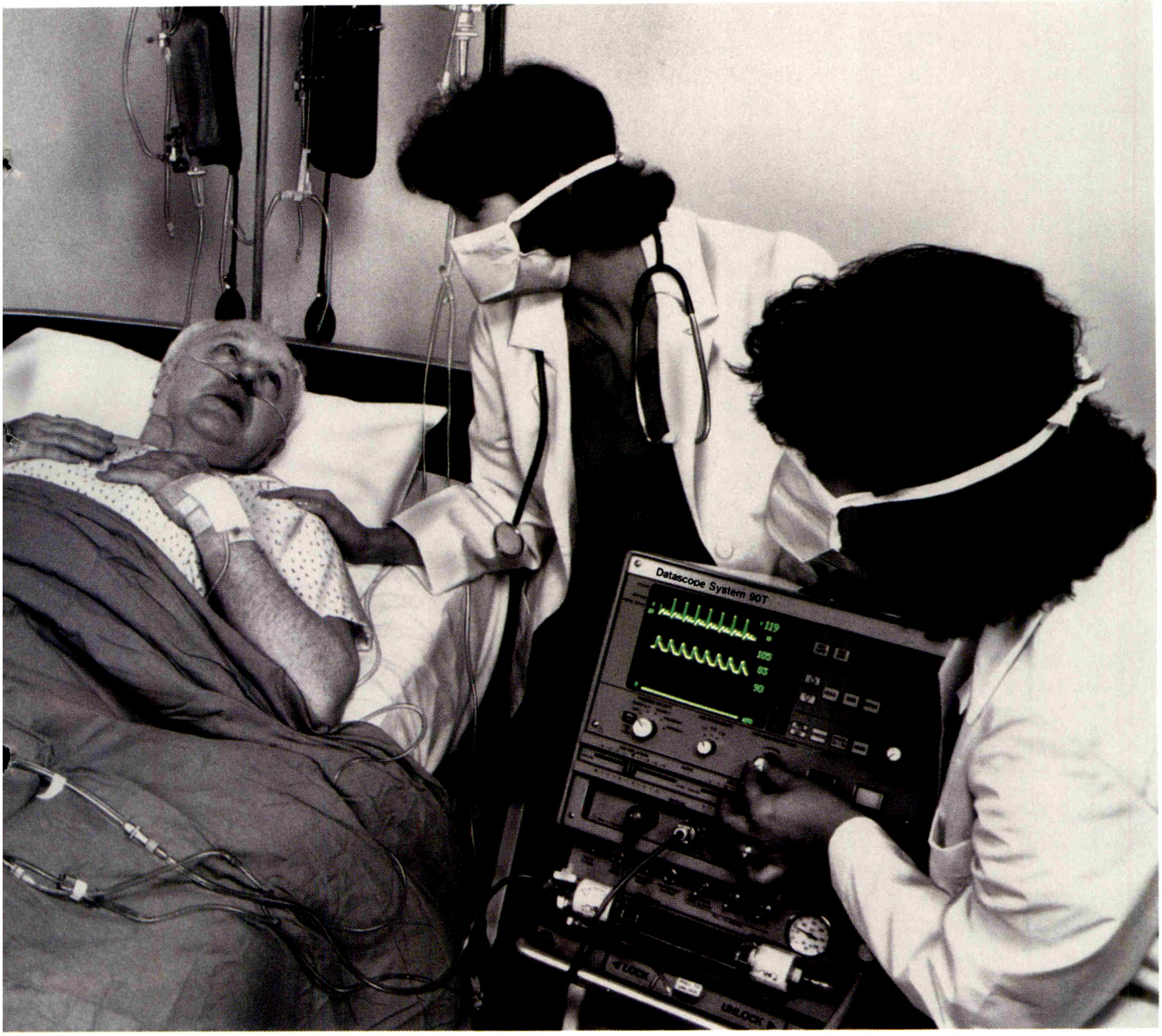

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Morrison C. Bethea, MD, and James L. Reynolds, MD

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Extended Use of a Pulmonary Homograft for Right Ventricular Outflow Tract Reconstruction
G. D. Angelini, MD, FRCS, and J. M. Quaegebeur, MD

Current Review

Free Radicals and Myocardial Protection: A Surgical Viewpoint
Philippe Menasché, MD, PhD, and Armand Piwnica, MD

Classics in Thoracic Surgery

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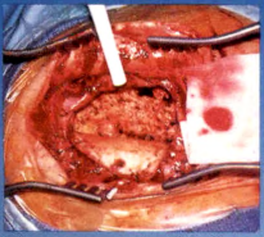
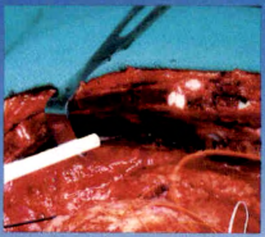
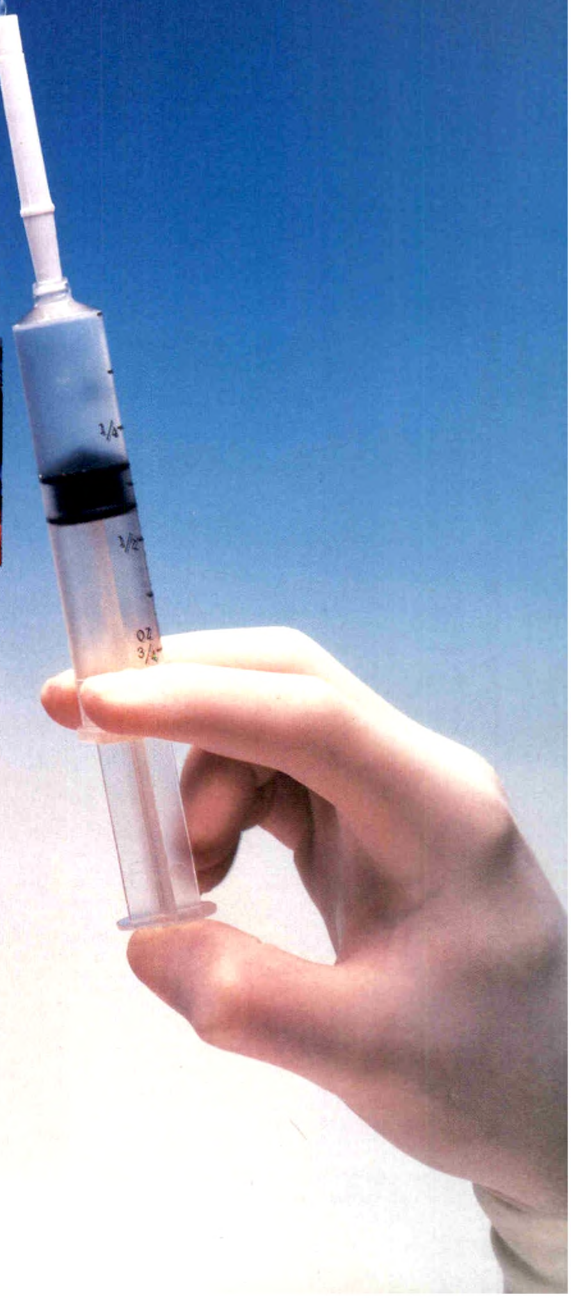


Easier delivery
In neurosurgery, provide hemostasis in hard-to-reach areas, such as deep tumor beds.



Sprays at any angle
In cardiovascular surgery, spray upside down to control oozing under the sternum.

Broad and even coverage
In burn surgery, cover large areas such as donor sites with an even and consistent spray.



INTRODUCING

Thrombin, Topical USP

THROMBOGEN*

Johnson & Johnson
PATIENT CARE, INC.

For further product information, call 800-526-2459.

Please see following page for brief summary of prescribing information.

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THROMBOGEN*
(THROMBIN, USP) (Bovine Origin)

Before prescribing, please see full prescribing information. A Brief Summary follows:
THROMBOGEN* must not be injected! Apply on the surface of bleeding tissue as a solution or powder.

INDICATIONS AND USAGE: THROMBOGEN* (Thrombin, USP) is indicated as an aid in hemostasis wherever oozing blood from capillaries and small venules is accessible.
In various types of surgery solutions of THROMBOGEN* may be used in conjunction with Absorbable Gelatin Sponge, USP for hemostasis.

CONTRAINDICATIONS: THROMBOGEN* is contraindicated in persons known to be sensitive to any of its components and/or to material of bovine origin.

WARNING: Because of its action in the clotting mechanism, THROMBOGEN* must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. THROMBOGEN* is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.
Pregnancy-Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.
Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: An allergic type reaction following the use of THROMBOGEN* for treatment of epistaxis has been reported. Febrile reactions have also been observed following the use of THROMBOGEN* in certain surgical procedures but no cause-effect relationship has been established.

DOSAGE AND ADMINISTRATION: General: Solutions of THROMBOGEN* may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc., solutions containing approximately 100 units per ml. are frequently used. For this, 10 ml. of diluent added to the 1,000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1,000 to 2,000 units per ml. may be required. For this the 5,000 unit vial dissolved in 5 ml. or 2.5 ml., respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use THROMBOGEN* (Thrombin, USP) in dry form on oozing surfaces.

Caution: Solutions should be used immediately upon reconstitution. However, the solution may be refrigerated at 2–8°C for up to three hours. The following techniques are suggested for the topical application of THROMBOGEN*:

1. The recipient surface should be sponged (not wiped) free of blood before THROMBOGEN* is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the THROMBOGEN* mixes freely with the blood as soon as it reaches the surface.
3. In instances where THROMBOGEN* in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried THROMBOGEN* is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.
   THROMBOGEN* may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:
   1. Prepare THROMBOGEN* solution of the desired strength.
   2. Immerse sponge strips of the desired size in the THROMBOGEN* solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
   3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

THROMBOGEN* Spray Kit: The THROMBOGEN* Spray Kit contains one sterile vial of THROMBOGEN*, one sterile vial of isotonic saline diluent, one sterile disposable syringe and one sterile syringe spray tip. The kit may be used as follows:

1. Remove the Tyvek† blister lid from the outermost tray by pulling up at the indicated corner. The sterile inner tray can then be lifted out or introduced into the sterile field.
2. Remove the Tyvek† blister lid from the inner tray to expose the sterile contents.
3. Using the sterile syringe equipped with the needle, draw the desired amount of saline diluent from the vial into the syringe.
4. Inject the saline diluent into the THROMBOGEN* vial from the syringe to reconstitute the THROMBOGEN* powder.
5. When the THROMBOGEN* is completely dissolved, draw the THROMBOGEN* solution into the syringe.
6. Remove and discard the needle; affix spray tip by pushing down and turning clockwise until the spray tip locks in place.
7. Depress the syringe plunger in a normal fashion to dispense the THROMBOGEN* solution through the tip in a fine spray.
8. Alternatively, to facilitate using the THROMBOGEN* with an Absorbable Gelatin Sponge, USP, the THROMBOGEN* solution may be dispensed directly from the syringe into a sterile container vs. attaching the spray tip. When THROMBOGEN* is needed in the dry form, the vial is opened and the dried THROMBOGEN* pellet should be broken up into a powder with a sterile glass rod or other suitable instrument.

Caution: Federal law prohibits dispensing without a prescription.

THROMBOGEN* is manufactured by GenTrac, Inc.
Middleton, WI 53562
*Trademark of Johnson & Johnson Patient Care, Inc.
†Trademark of DuPont.
Store at normal controlled room temperature, except 1,000 unit vial of THROMBOGEN*, which must be stored between 2°–8°C (36°–46°F).
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- ☐ Type manuscript double-spaced throughout (including title page, abstract, text, references, tables, and legends) on one side only on 22 × 28 cm (8½ × 11 inch) opaque bond paper with 3 cm (1¼ inch) margins all around. *This also applies to correspondence.* Type the last name of the first author in the upper right-hand corner of each page, including the title page.
- ☐ Arrange manuscript as follows: (1) title page, (2) abstract, (3) text, (4) references, (5) tables, and (6) legends. Number pages consecutively, beginning with the title page as page 1 and ending with the legend page.
- ☐ A manuscript for an *original article* ordinarily should not exceed 26 double-spaced typewritten pages, and should be proportionally shorter the more illustrations and tables that are included.
- ☐ The *text* for case reports should be *no more* than 4 double-spaced typewritten pages. If tables or illustrations are included, the text must be reduced. The text for a "how to do it" article should be even briefer, but with detailed illustrative material. Case reports and "how to do it" articles that exceed the allowable length will not be considered for publication.
- ☐ Referencing should be selective and pertain directly to the work being reported. Except in collective and current reviews, comprehensive listings serve no useful purpose and utilize valuable space. As a general guide, original articles should have no more than 20 references; case reports, 8 references; and "how to do it" articles, 5 references.

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- ☐ Give the paper as short a title as possible. Also submit a short title of 3 or 4 words to be used as a running head. Include only the names of the authors directly affiliated with the work, stating for each the highest academic degree. Include the name and location of no more than two institutional affiliations.
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- ☐ Generally, the text should be organized as follows: Introduction, Material and Methods, Results, and Comment.
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- ☐ Type acknowledgments, including complete grant or subsidy information, at the end of the text before the references.

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- ☐ Journal references should provide *inclusive* page numbers; book references should cite *specific* page numbers.
- ☐ Double-check references for accuracy, completeness, and nonduplication.

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Journal Article

8. Diehl JT, Eichhorn EJ, Konstam MA, et al. Efficacy of retrograde coronary sinus cardioplegia in patients undergoing myocardial revascularization: a prospective randomized trial. Ann Thorac Surg 1988;45:595–602.

(List *all* authors if 6 or fewer; otherwise list first 3 and add "et al.")

Chapter in Book

12. Katz PO. Achalasia. In: Castell DO, Richter JE, Dalton CB, eds. Esophageal motility testing. New York: Elsevier Science Publishing Company, 1987:107.

Book (Personal Authors or Editors)

18. Larone DH. Medically important fungi: a guide to identification. 2nd ed. New York: Elsevier Science Publishing Company, 1987.

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The next crucial step:
raising output without
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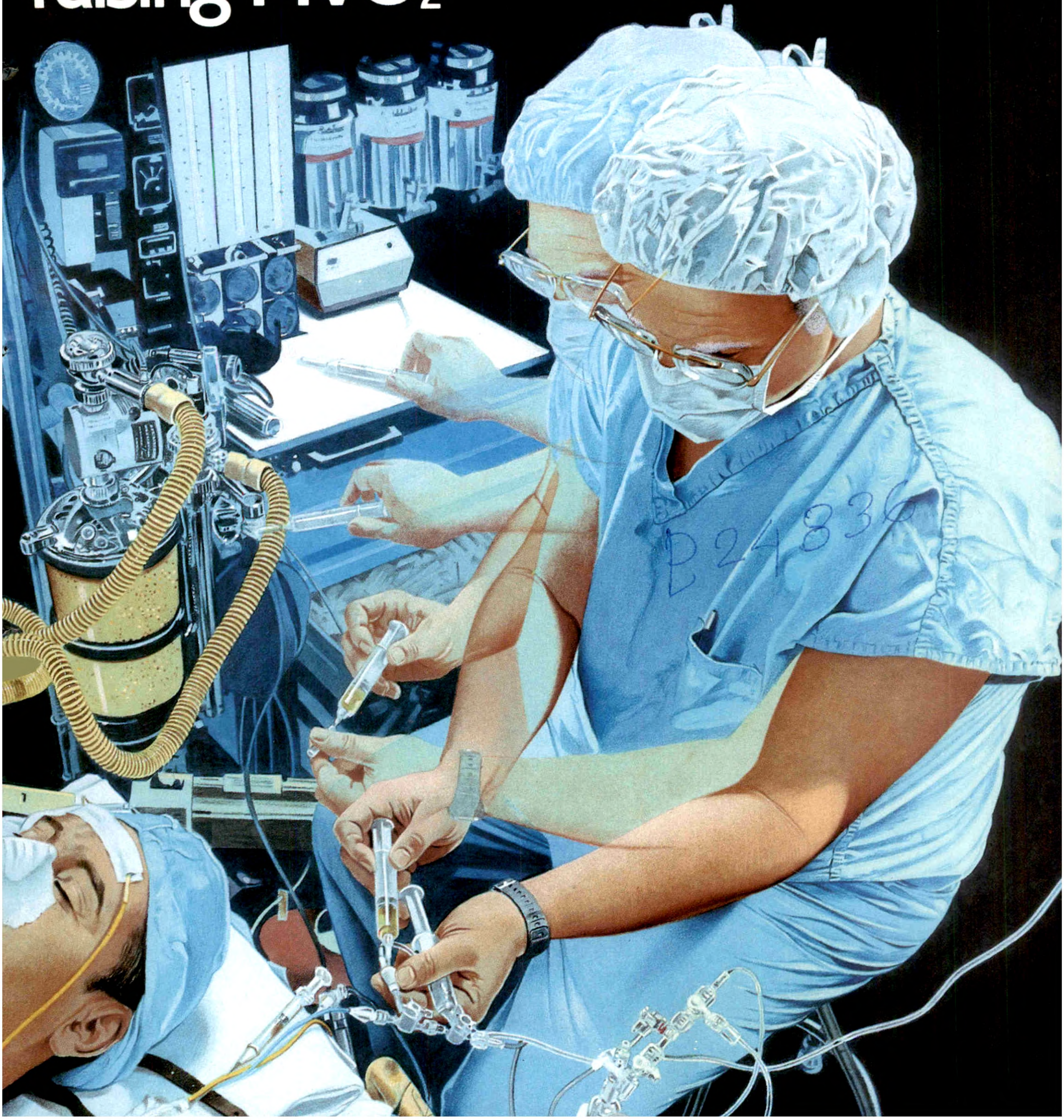

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A crucial step i
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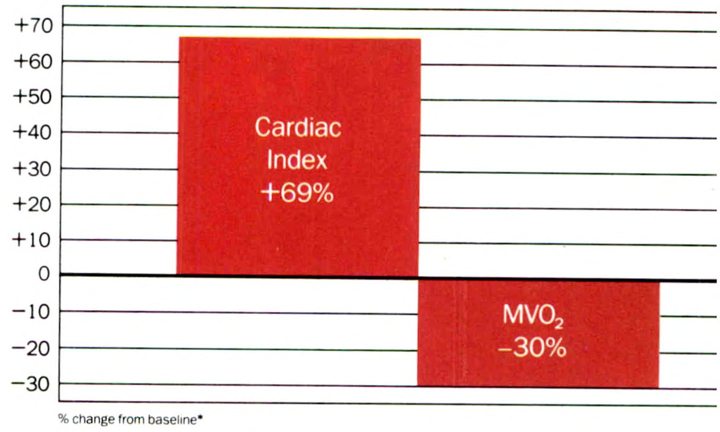
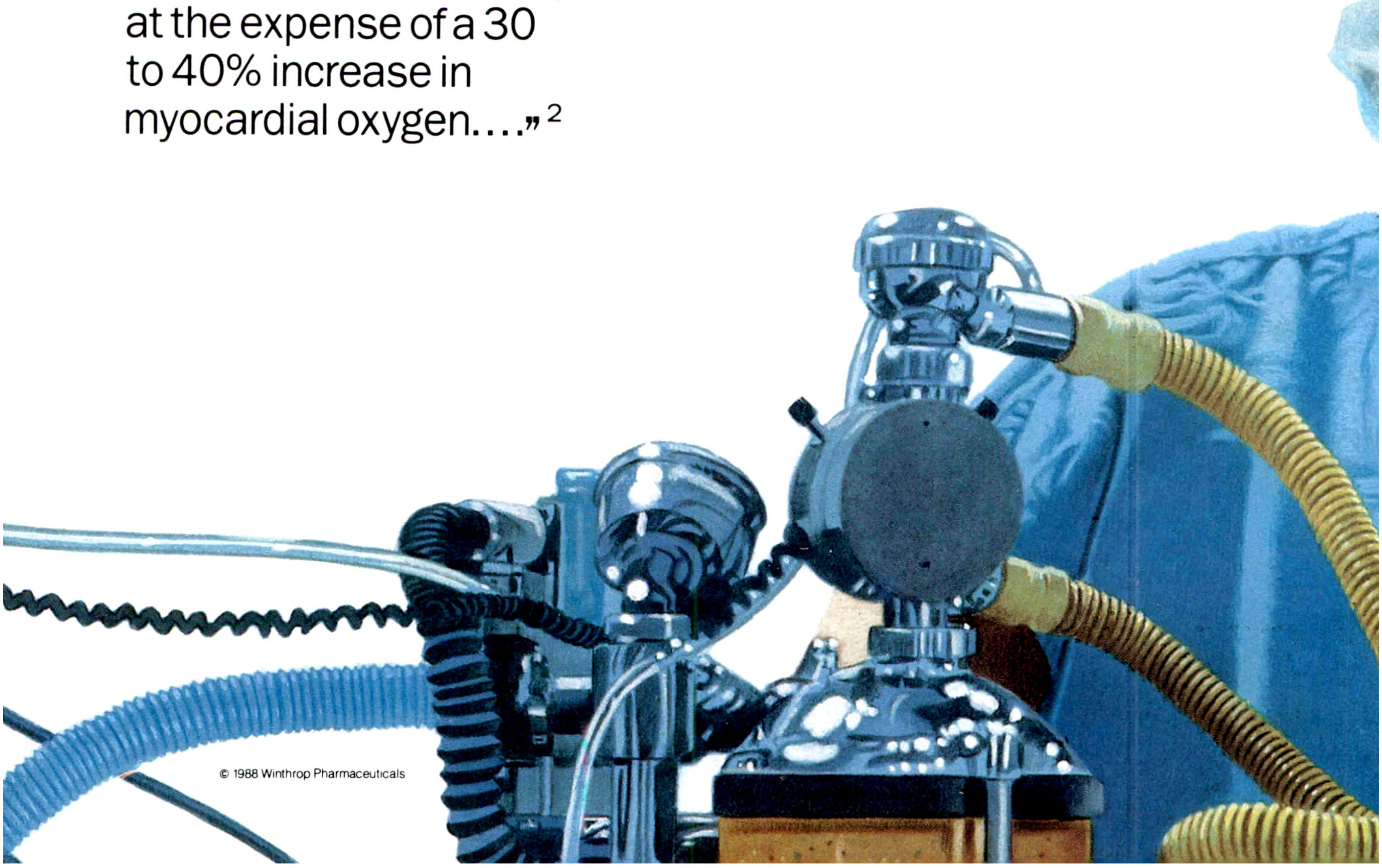


"…hemodynamic improvements with catecholamine agents such as dobutamine tend to be achieved only at the expense of a 30 to 40% increase in myocardial oxygen…."[2]

*n=8. Adapted from Benotti et al.[1] Amrinone was infused in patients with severe congestive hea failure due to coronary artery disease at 2.5 mg/kg over 1 hour.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to corona artery disease. *Circulation* 1980;62:28–34.

2. Baim DS: Effects of amrinone on myocardial energetics in severe congestive heart failure. *Am J Cardiol* 1985;56:16B–18B.



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- Unique mechanism of action—PDE III inhibition
- Significantly improves pulmonary hemodynamics
- Efficacy maintained even in patients on beta blockers
- Does not increase the risk of arrhythmias (see Precautions)

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Inocor® I.V.
(AMRINONE)
Raises output without raising MVO$_2$

Please see following page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

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- No effect on platelet function
- No significant increase in risk of arrhythmias (see Precautions)
- Safe and effective when used concomitantly with intravenous or inhaled anesthetics
- Unlike catecholamines, does not act on the beta receptors—may be used effectively in patients on beta blockers

Brief Summary

Please consult full product information before prescribing. A summary follows. INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it. It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

INOCOR is not recommended for use in acute myocardial infarction.

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides; lidocaine, quinidine; metoprolol, propranolol; hydralazine, prazosin; isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone; captopril; heparin, warfarin; potassium supplements; insulin; diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® (disopyramide) should be undertaken with caution.

CHEMICAL INTERACTIONS A chemical interaction occurs slowly over a 24-hour period when the intravenous solution of INOCOR lactate injection is mixed directly with dextrose (glucose)-containing solutions. **THEREFORE, INOCOR LACTATE INJECTION SHOULD NOT BE DILUTED WITH SOLUTIONS THAT CONTAIN DEXTROSE (GLUCOSE) PRIOR TO INJECTION.**

A chemical interaction occurs immediately, which is evidenced by the formation of a precipitate when furosemide is injected into an intravenous line of an infusion of amrinone. Therefore, furosemide should not be administered in intravenous lines containing amrinone.

USE IN PREGNANCY *Pregnancy category C:* There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

USE IN CHILDREN Safety and effectiveness in children have not been established.

ADVERSE REACTIONS *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below $100{,}000/mm^3$ or normal limits in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions:* Asymptomatic platelet count reduction (to less than $150{,}000/mm^3$) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than $150{,}000/mm^3$ occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone, reduce dosage, or discontinue the drug based on the usual benefit-to-risk considerations.

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

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NOTE: Parenteral drug products should be inspected visually and should not be used if particulate matter or discoloration is observed.

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The "Incomplete" Resection

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For many years the term *palliative resection* was used to denote those instances when there was either less than total removal of all gross tumor in the ipsilateral hemithorax in the lung cancer patient or the resection had been carried out in the presence of known distant metastases. Fortunately, the use of this inappropriate term has fallen into disfavor for few, if any, patients are truly palliated by removal of the lung when cure is not the goal. Most, albeit not all, local symptoms can be relieved by less invasive and less physiologically damaging modalities. In its place the more appropriate term *incomplete resection* has come into common usage. As with many terms, however, its meaning is obscured by conceptual misunderstanding.

Various reports in the literature define the term loosely or on theoretically but unproved concepts. In the recent article by Nakahashi and colleagues [1], an incomplete resection was defined as a simple lobectomy, segmentectomy, or wedge resection with residual disease, yet in their patients classified as having an incomplete resection of T3 N0 disease there was a 27% 5-year survival, which was essentially no different than the 34% 5-year survival recorded for those with complete resections. Obviously, the "incompleteness" of a number of the resections was based on loose criteria. There were, however, no long-term survivors with incomplete resection of T3 N1 or T3 N2 disease.

The North American Lung Cancer Study Group [2] has chosen to define one criterion, among others, of an incomplete resection as the presence of metastatic tumor in the highest resected ipsilateral superior mediastinal node, although no gross or microscopic residual disease is documented to be remaining in the ipsilateral hemithorax. Yet a resected metastically involved subcarinal node is not considered to represent an incomplete resection. Nohl-Oser [3], Greschuchna and Maassen [4], and Hata and associates [5], however, have convincingly shown that spread from this nodal station to the contralateral superior mediastinal lymph nodes, more so from left to right, occurs in approximately 20% or more of all such patients. The completeness or incompleteness relative to involvement of the pulmonary ligament lymph nodes or inferior paraesophageal nodes is not even considered. Such an arbitrary criterion as adopted by this group can potentially lead to great variations in the data base that is used to compare treatment results.

It is more appropriate to strictly define an incomplete resection as one documented by histological proof of residual gross tumor or microscopic tumor at one of the margins of the resected specimen or the presence of tumor cells in an associated pleural effusion. With such criteria more meaningful data can be obtained.

I [6] reported that with such criteria, 74% of 221 patients who underwent an incomplete resection as defined had died by the end of the first year, 8.5% survived for 3 years, and only 4% survived 5 years or more. This latter group represented primarily the survivors in a small subset of patients whose residual disease consisted only of microscopic submucosal (nonlymphatic) disease in the distal cut end of the bronchial stump, who had a 5-year survival rate of 23%. A similar subset of patients also was identified by Jeffery [7] and Soorae and Stevenson [8]. With the exception of this subset, all other patients, except 4 with only microscopic extension to a resected margin, died within 3 years. These 4 patients represented an overall 5-year survival rate of only 2%. Abbey Smith [9] identified a second favorable subgroup, those with residual tumor left on the atrial wall. Three of 7 patients survived 5 years, but no other patients with incomplete resections did so. This observation unfortunately has not been confirmed by others.

Hara and colleagues [10], however, reported no survival in patients with an incomplete resection of stage III disease, and Burt and associates [11], at Memorial Hospital, also recorded no survival in patients with incompletely resected stage III disease with mediastinal extension treated by surgical excision only. Patterson and associates [12], in a highly selected population with incomplete resections, reported 1 of 12 patients to have survived 5 years, but the site of microscopic residual disease was unspecified.

It would seem, therefore, based on the aforementioned data, that a strict definition of an incomplete resection should be established. This definition should be based on histological proof of residual disease being present in the ipsilateral hemithorax. Whether the residual disease was macroscopic or microscopic only and the site of such involvement should also be noted. In the absence of such documentation, all other resections should be considered complete and potentially curative in intent. It is not acceptable to judge a resection as incomplete because a complete lymph node dissection has not been done or because the surgeon believes on a theoretical basis that the patient has a poor prognosis.

With adherence to this strict definition, more meaningful data will become available for comparison of treatment results and the evaluation of alternate multimodality treatment regimens.

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Mortality Rates and Risk Factors in Coronary Bypass Surgery

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Nothing in surgical practice is as constant as change. New knowledge and technology make operations safer and more effective. Better results elevate the expectations of both patients and physicians, causing operative indications to be extended. New treatment indications arise and old ones are modified by emerging nonsurgical therapies. These influences are particularly strong in coronary bypass surgery as described by Davis and colleagues in this issue [1].

This retrospective survey of surgical experience is of a type that has become common in our literature. Such studies are conducted partly because the data already exist. One chooses an interesting clinical question that seems to be answerable from the data at hand and proceeds through analysis to draw conclusions. Scientific purists may scoff, but such studies are useful because they provide information about patients that is obtainable in no other practical way. Although the data may stand alone, the conclusions that Davis and colleagues place upon them require considerable critical interpretation by readers because of the post hoc assumptions that, necessarily, have been applied.

One assumption of this study is that interventional cardiology has changed the type of patient needing a bypass operation. Although the characteristics of the study patients certainly changed during the two time periods surveyed, the extent to which these changes are attributable to angioplasty is arguable. For example, the increasing age of bypass patients is a constant trend evident since the early 1970s; it is also more likely to be the cause of the increase in comorbid factors such as diabetes and hypertension than is angioplasty. Similarly, with results as good as those reported from the earlier period, it would be surprising if the authors, themselves, had not extended coronary bypass surgery to older and sicker patients in the later period.

Finally, the impact of the Coronary Artery Surgery Study should not be underestimated. The Coronary Artery Surgery Study failed to document significant survival benefit for patients with mild angina and single- or double-vessel disease and noted a trend toward fewer operations for all patients with less than triple-vessel disease at participating clinical sites before publication of the randomized trial. The major impact of the randomized trial on surgical referrals followed its publication in 1983, 2 years after the close of the first period in the report by Davis and associates and 2 years before the opening of the second. Perhaps angioplasty, instead of subtracting patients who would have been considered surgical candidates, simply offered revascularization to some patients who would otherwise have been treated noninvasively. The study data support this view equally well.

Having demonstrated that their patients changed in ways that would seem to increase the risk of coronary bypass operations, Davis and colleagues evaluated outcome mainly through operative mortality during the two periods and found a slight increase in the later period, which was not statistically significant. When overall operative mortality approaches a level as low as 3% it becomes insensitive as an outcome measurement and is likely to change little without either far more drastic changes in patient characteristics or vast improvements in treatment. We are told that hospital stay was longer in the later period and complications somewhat more frequent. However, for a fuller evaluation of treatment effectiveness in an increasingly sicker group of patients we need additional outcome measurements, especially those that can influence long-term results such as perioperative myocardial infarction and, although beyond the scope of the study, patient status beyond the postoperative interval.

The most dangerous risk factor in this study is an emergency operation. The management challenge of today is the acutely ischemic patient who requires an urgent operation. This includes the patient with impending or ongoing myocardial infarction, either natural or iatrogenic, the patient with myocardial ischemia at rest despite drug therapy, and the small, elderly, hypertensive patient with unstable symptoms, among others. Given standard operative techniques and competent hospital care, the proportion of such patients in a surgical practice is likely to influence results more than anything else and, as Davis and colleagues have shown, this proportion seems to be rising.

Much attention has been directed recently to coronary bypass mortality rates by the annual release of data on Medicare patients by the Health Care Financing Administration (HFCA). This has resulted in the spectacle of hospitals listed in the newspapers in rank order according to small percentage differences in coronary bypass mortality rates and in the distasteful and self-serving use of such lists in health care advertising. This information is made available by the government under the guise of helping the public to make informed health care choices. If the case mix of coronary bypass patients in all hospitals was identical, and if the public understood that most of the difference in published rates was caused by random variation in results rather than by treatment effectiveness, then the release of raw mortality data might be considered

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a useful public service. However, as neither is true, the practice is analogous to placing a slightly dangerous toy in the hands of a child and asking it to choose whether to play.

An even more ambitious program to define the effectiveness of health care, and coronary revascularization in particular, has been described by Dr William Roper, head of the HFCA, and his colleagues [2]. This plan will link information from Medicare claims with clinical data abstracted from medical records by the Professional Review Organizations. Conclusions on the efficacy and "appropriateness" of treatment will be formed from these data and will be given to physicians, patients, and health care organizations in an effort to improve the general standard of medical practice.

This is a laudable goal, but it is equally clear that the HFCA may use its conclusions to help define approved services for Medicare beneficiaries. Given the political pressures to reduce health care expenditures, can we rely on HFCA data and interpretations alone to protect the access of our patients to necessary medical services including coronary bypass? I think not.

The Society of Thoracic Surgeons is presently attempting to establish a national data registry in which its members may concurrently enter data from their practices on operative techniques, patient risk factors, and outcomes. Analytical methods will be applied to describe national practice patterns and will be made available so that individual surgeons can evaluate their own experience. This is a task of great difficulty that will require the efforts of each of us, yet it is imperative that it be successful. We owe it to our patients.

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Truncus Arteriosus

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Truncus arteriosus (TA) is an uncommon (0.043/1,000 live births) and complex congenital cardiovascular malformation; furthermore, approximately 20% of patients with this condition are born prematurely. Consequently, TA has posed and continues to pose a serious therapeutic challenge. The history of the surgical treatment of TA is linked to the development of palliative and reparative operations for other, more common congenital cardiac defects. After Muller and Dammann introduced the concept of banding of the pulmonary artery (PAB) in 1952, banding of one or both pulmonary arteries was adapted for TA in the early 1960s. However, operative mortality of PAB for TA exceeded 50% in most institutions. Of the survivors, a large percentage developed pulmonary vascular obstructive disease because of inadequate PAB, or substantial iatrogenic deformation or even complete obstruction of one or both pulmonary arteries.

Repair of truncus arteriosus became possible with the development of conduits to bridge the gap between the right ventricle and the detached pulmonary arteries. Klinner, in 1961, was the first to use a nonvalved Teflon graft in a repair of tetralogy of Fallot and pulmonary atresia. One year later, Sloan and associates, at The University of Michigan, succeeded in repairing TA using a nonvalved plastic conduit. Subsequently, McGoon and Rastelli at the Mayo Clinic accumulated a large experience with repair of TA using a valved homograft. However, this operation was applied predominantly to a group of older children who had survived PAB and had retained suitable pulmonary artery anatomy and physiology or to an even smaller number of patients who had congenital stenosis of the origin of one or both pulmonary arteries and hence a protected pulmonary vascular bed. Also included were a few exceptional patients who had unrestricted high-pressure, high-volume pulmonary blood flow but who, for unknown reasons, did not develop pulmonary vascular obstructive disease. Clearly, these patients represented only a small minority of children born with TA. It became obvious that to make an impact on survival of children born with TA, efforts had to be directed toward early repair in infancy. In 1971, Barrat-Boyes and associates, using hypothermic circulatory arrest, accomplished the first successful repair in infancy of TA in a 6-week-old baby. This important breakthrough was unfortunately followed by a period of continued high operative mortality with this operation until Ebert and associates reported their impressive results with repair of TA in a large group of infants. This encouraging experience soon exerted its catalytic effect on other institutions. By 1989, the results of repair of TA have greatly improved in many centers; however, optimal timing of operation and management of associated lesions, particularly truncal valve regurgitation, remain controversial.

The contribution by Bove and associates from The University of Michigan [1] represents an additional important step forward in the surgical management of this complex malformation. The authors report on 11 patients with TA, 8 of whom were repaired as neonates. This significant feat was accomplished with only 1 operative death, which is even more remarkable considering that 2 neonates had successful truncal valve replacement. The use of an aortoventriculoplasty (modified Konno technique) to amplify the aortic valve area in these neonates is ingenious. This series also includes a patient with successful repair of TA complicated by nonconfluent pulmonary arteries. In our own experience, my colleagues and I have encountered 5 patients with TA and interrupted aortic arch and 2 other patients with TA and a complete atrioventricular canal. Multiple ventricular septal defects and various types of anomalous pulmonary or systemic venous connections can render repair more difficult. Because of the not infrequent coexistence of these complex anomalies, the low mortality for repair of TA as reported by Bove and associates may be difficult to consistently duplicate.

We concur with Bove and associates that the use of cryopreserved valved homografts (aortic or pulmonary) has markedly facilitated repair of this lesion. Dacron conduits were occasionally difficult to fit in the small mediastinum of neonates without causing kinking of one or both pulmonary arteries, and occasionally suturing of this stiff material to the tenuous pulmonary arteries proved technically demanding. Despite a very large experience with the use of valved homografts in neonates, infants, and children, we have so far not recognized a graft versus host reaction, a diagnosis suspected by Bove and associates in a child who died 3 months after operation. Because of the rarity of this condition, it is regrettable that they did not include more of the information on which they based this diagnosis.

We strongly support their recommendation that repair of TA should be performed as early as possible after diagnosis, ideally within the first 2 months of life. We also agree that if clinically feasible, one should postpone repair until neonatal pulmonary vascular resistance falls, generally after the first 2 weeks of life. As, in our experience, we have encountered such a high incidence of clinically significant additional defects, we still advocate both a preoperative two-dimensional echocardiographic or Doppler examination and cardiac catheterization. The impressive results reported by Bove and associates with success-

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ful truncal valve replacement in neonates encourages us to be more aggressive in the future in recommending prosthetic or homograft valve replacement in patients with severe truncal valve regurgitation. Until now, this subset of patients has carried a very high perioperative mortality.

Bove and associates must be congratulated for their excellent results with repair of TA in neonates. This important contribution is in keeping with the tradition of innovation established for this lesion by The University of Michigan team.

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Mortality of Coronary Artery Bypass Grafting Before and After the Advent of Angioplasty

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In an effort to determine whether the population of patients undergoing isolated coronary artery bypass grafting and the outcome of these operations have changed, we analyzed the records of two patient populations from our institution. Interventional cardiology techniques (angioplasty, thrombolysis) were not used at our institution before 1982. The records of 736 patients (group 1) who underwent isolated coronary artery bypass grafting from January 1975 to July 1981 were reviewed and compared with a group of 603 patients (group 2) who underwent operation from July 1985 to December 1987. The techniques of operation and myocardial preservation were virtually identical during the two periods. During the group 2 analysis period, 343 angioplasty procedures were performed. The patients in group 2 were significantly older, had increased preoperative New York Heart Association classification, had sustained more previous myocardial infarctions, and had more associated morbid medical conditions. There was a threefold increase in patients seen for reoperative revascularization procedures and a fourfold increase in emergency operations. Overall mortality, although not significantly different, did increase slightly from 2.69% in group 1 to 3.83% in group 2. Mortality after elective procedures remained essentially unchanged (2.05% for group 1 and 1.90% for group 2).

(Ann Thorac Surg 1989;47:493–8)

With the increasing use of interventional cardiology procedures, it has been suggested that mortality rates for coronary artery bypass grafting (CABG) have increased over the past 10 years and that the type of patient needing a bypass operation has changed. To determine whether the population of patients undergoing isolated CABG and the outcome of these operations have been altered by the expanded options in interventional cardiology, we analyzed the records of two patient populations from our institution. The records of patients who underwent isolated CABG between 1975 and 1981, a time before the use of angioplasty at our institution, were compared with those of patients who underwent isolated CABG between 1985 and 1988, a period when angioplasty was routinely performed.

Material and Methods

Interventional cardiology techniques, including angioplasty and thrombolysis, were not used at our institution before 1982 but were in routine use by 1985. The records of 736 patients (group 1) who underwent isolated CABG between January 1975 and July 1981 were retrospectively reviewed and compared with those of a group of 603 patients (group 2) who underwent the same operation between July 1985 and December 1987. Patients having emergency as well as elective operations were included. No other cardiac procedures, such as valve replacement, were performed on these patients. Preoperative cardiac catheterization and coronary arteriography were done on all patients, and CABG was carried out for all angiographically significant lesions (more than 70% luminal narrowing). Hemodynamic and anatomical data were gathered from cardiac catheterization.

Clinical data including age, sex, and preoperative and postoperative New York Heart Association functional classification were abstracted. Important historical considerations such as previous myocardial infarction, coexisting diabetes, hypertension, prior angioplasty, or prior CABG were recorded. Whether the operation was done electively or emergently was also noted. An emergency operation was defined as one performed within 24 hours of catheterization because of evolving myocardial infarction with cardiogenic shock or cardiac arrest, failed percutaneous transluminal coronary angioplasty (PTCA) with evolving myocardial infarction, or chest pain unrelieved by medical therapy. In addition, patients who had undergone previous PTCA were looked at separately. The use of intraaortic balloon counterpulsation in the emergency group was also noted.

In both groups, cardiopulmonary bypass was performed using a roller pump, membrane lung or bubble oxygenator, and moderate systemic hypothermia (20° to 25°C). Topical cooling in conjunction with multidose crystalloid cardioplegic solution infused through the aortic root provided myocardial protection. Preoperative and postoperative monitoring included the routine use of

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Swan-Ganz pulmonary artery catheters to evaluate filling pressures as well as thermodilution cardiac output.

The technical considerations analyzed included the number of distal coronary anastomoses performed as well as the need for postoperative intraaortic balloon pump support. Operative mortality was defined as death within 30 days after operation or death prior to discharge, and was applied to both groups of patients regardless of whether the operation was elective or an emergency.

Results

Preoperative patient analysis documented significant changes in the profiles of patients who underwent CABG (Table 1). The mean age of the patients in group 2 increased by 5.6 years, and 38% were older than 65 years; in group 1, only 11% were more than 65 years old. Although there was a higher percentage of women in group 2, the difference was not significant. Preoperative risk factors including previous myocardial infarction, hypertension, and diabetes were present in a significantly higher percentage of patients in group 2. This cohort also had significantly worse preoperative symptoms as evidenced by a greater percentage of patients with New York Heart Association functional class III or IV symptoms and the fact that only 4.4% of group 2 patients had class I or II symptoms before operative intervention as opposed to 37.2% of group 1 patients.

Preoperative hemodynamic variables obtained at the time of cardiac catheterization demonstrated little physiologically significant difference between the two groups, except for a mild increase in left ventricular end-diastolic pressure in group 2 (Table 2). However, anatomical analysis revealed a marked trend toward multiple-vessel disease, especially triple-vessel disease, in group 2.

Operative data are presented in Table 3. A fourfold rise in the number of patients undergoing emergency CABG was seen, with a consequent rise in preoperative intraaortic balloon pump or femorofemoral artery cardiopulmo-

Table 1. Preoperative Patient Analysis[a]

Variable	Group 1 (n = 736)	Group 2 (n = 603)	*p* Value
Age (yr)	55.50 ± 0.32	61.06 ± 0.39	0.001[b]
Older than 65 years	10.87	38.14	0.001[c]
Sex			NS
Male	83.17	79.60	
Female	16.83	20.40	
Risk factors			
Hypertension	15.91	38.54	0.001[c]
Diabetes	4.38	21.93	0.001[c]
Previous MI	27.05	52.16	0.001[c]
NYHA Class			0.001[c,d]
I	11.96	0.33	
II	25.22	4.02	
III	44.81	74.54	
IV	18.01	21.11	
Repeat CABG	1.91	6.31	0.001[c]

[a] Unless otherwise indicated, data are shown as percentages. [b] Student's *t* test was used. [c] The Pearson χ^2 test was used. [d] Analysis revealed a significantly different distribution of patients in NYHA functional classes between the two groups.

CABG = coronary artery bypass grafting; MI = myocardial infarction; NS = not significant; NYHA = New York Heart Association.

Table 2. Preoperative Hemodynamic and Anatomical Variables[a]

Variable	Group 1	Group 2	*p* Value
Cardiac index (L/min/m^2)	2.64 ± 0.02	2.69 ± 0.03	NS
Ejection fraction	0.56 ± 0.01	0.57 ± 0.01	NS
LVEDP (mm Hg)	15.86 ± 0.29	16.70 ± 0.31	0.333[b]
No. of diseased vessels	2.00 ± 0.05	2.62 ± 0.02	0.001[b]
One	32.13%	3.65%	0.001[c]
Two	35.38%	31.18%	
Three	32.49%	65.17%	

[a] Where applicable, data are shown as the mean ± the standard error of the mean. [b] Student's *t* test was used. [c] The Pearson χ^2 test was used.

LVEDP = left ventricular end-diastolic pressure; NS = not significant.

Table 3. Operative Data[a]

Variable	Group 1	Group 2	*p* Value
No. of grafts	2.67 ± 0.04	3.35 ± 0.04	0.001[b]
Type of graft			
Saphenous vein	100.00%	50.41%	
IMA ± saphenous vein	0%	49.59%	
Emergency	2.70%	12.77%	0.002[c]
MI with shock or arrest	0/19	18/77	
Failed PTCA, evolving MI	0/19	16/77	
Refractory angina	19/19	40/77	
Elective	97.30%	87.23%	
Preoperative assist			0.001[c]
None	723	574	
Intraaortic balloon pump	10	27	
Femorofemoral	0	3	
Postoperative assist			0.050[c]
None	698	559	
Intraortic balloon pump	33	43	
Ventricular assist device	3	1	
Bypass time (min)	115.05 ± 1.76	112.84 ± 1.47	NS
Cross-clamp time (min)	61.76 ± 0.96	67.08 ± 0.95	0.001[b]

[a] Where applicable, data are shown as the mean ± the standard error of the mean. [b] Student's *t* test was used. [c] The Pearson χ^2 test was used.

IMA = internal mammary artery; MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

Table 4. Operative Mortality and Morbidity

Variable	Group 1	Group 2	*p* Value
Mortality			
Elective	2.05%	1.90%	NS
Emergency	15.79%	16.88%	NS
MI with shock or arrest	0/0	8/18	
Failed PTCA, evolving MI	0/0	3/16	
Refractory angina	3/19	2/40	
Overall	2.69%	3.83%	NS
Complications			
Hemorrhage	4.23%	2.64%	NS
Sternal infection	2.63%	4.28%	NS
Respiratory failure	0.55%	0.33%	NS
Postsurgical hospitalization (days)[a]	8.00 ± 0.17	11.17 ± 0.81	0.001[b]

[a] Data are shown as the mean ± the standard error of the mean. [b] Student's *t* test was used.

MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

nary bypass support. The number of patients who required postoperative support with an intraaortic balloon pump increased dramatically. There was a significant increase in the number of distal anastomoses performed in group 2 compared with group 1, although total bypass times and cross-clamp times were similar. Patients undergoing myocardial revascularization for a second time, rare in the earlier group of patients, increased to 6.31% in the later group of patients.

Operative mortality and morbidity are shown in Table 4. Despite the changes previously noted in patient characteristics preoperatively, overall operative mortality did not change significantly. Survival after emergency operations was much worse than that after elective operations in both groups of patients. Mortality rates after elective procedures remained essentially unchanged at approximately 2%. Morbidity for isolated CABG did not change significantly. The patients in group 2 had more sternal wound infections, and the group as a whole required considerably longer hospitalization, but they had fewer complications related to pulmonary failure.

The outcome for patients with a history of prior angioplasty is presented in Table 5. Thirty-six patients ultimately underwent operative intervention after one or more PTCA attempts during the group 2 analysis period. Sixteen of these patients went directly to the operating room from the catheterization laboratory because of an evolving myocardial infarction after a PTCA complication. The mortality in this group was 18.75%. A large portion (36.1%) of the patients who underwent PTCA and then required surgical intervention were found to have triple-vessel coronary artery disease.

Comment

Surgical management of coronary artery disease has undergone a remarkable evolution over the past 15 years. Advances in myocardial protection, recognition of the importance of complete revascularization, and increased utilization of the internal mammary artery as a conduit have dominated the technical aspects of this evolution. However, it has been suggested that operative mortality rates may, in fact, be worsening despite our improved understanding of the technical considerations of performing CABG [1]. Two possible reasons for this are an expanded role for CABG (more patients with more comorbid conditions) and the advent of angioplasty as a routine therapeutic method for certain patients with less complex coronary artery disease who previously would have been treated surgically. Concern over whether CABG mortality and morbidity rates have changed at our institution over the past decade and whether the advent of angioplasty has had a significant impact on mortality from operation prompted this retrospective analysis.

It has been suggested that the preoperative characteristics of the patient undergoing isolated CABG have been changing since the advent of angioplasty [2]. Some of these changes have been noted by others to be determinants of increased operative risk. The Coronary Artery Surgery Study by Myers and associates [3] suggested that age of more than 60 years, female sex, and emergency operation were all associated with increased operative mortality. In addition to these factors, incomplete myocardial revascularization was found by Cosgrove and colleagues [4] to adversely affect survival. Junod and colleagues [5], in their analysis of 913 patients having isolated CABG, found that only women demonstrated a significant difference in operative mortality among patients older than 70 years. Most of the deaths in their study occurred in women undergoing emergency operation. The problem of increased incidence of associated medical disease in the contemporary patient having isolated CABG was demonstrated by Naunheim and coworkers [1]. This factor has been shown to worsen operative mortality in patients older than 65 years undergoing isolated CABG [6].

Our experience parallels previous series in showing a trend toward more operations for older patients, a growing percentage of female patients, more patients with associated medical problems, more reoperative procedures, and more emergency procedures. All of these

Table 5. Outcome for Patients Undergoing Percutaneous Transluminal Coronary Angioplasty[a]

Outcome	No. of Patients	Operation		
		Emergent	Urgent	Elective
Ultimate CABG	36	16	4	16
1-Vessel disease	4	3	0	1
2-Vessel disease	19	8	4	7
3-Vessel disease	13	5	0	8
Mortality	3 (8.33%)	3/16	0/4	0/16

[a] A total of 343 percutaneous transluminal coronary angioplasties were performed.

CABG = coronary artery bypass grafting.

factors define a patient pool with increased operative risk. Fifty-two percent of our group 2 patients had sustained documented myocardial infarction before being selected for isolated CABG compared with 27% in group 1. A marked trend toward more advanced coronary artery disease is demonstrated by the twofold increase in patients with triple-vessel disease seen for isolated CABG in group 2. This parallels the experience of others [1, 2]. Overall ventricular function was not seen to have been worse, however, in the group 2 patients. Ventricular function in the patients in group 2 who died was significantly worse than in the group as a whole. Of the 9 patients having an elective operation who died, 4 had a preoperative cardiac index of less than 2 L/min/m^2, and 5 had an ejection fraction of less than 35%.

Numerous reports [1, 7–9] have demonstrated a progressive increase in the number of patients having reoperation for coronary revascularization. There are technical problems inherent in performing reoperative myocardial revascularization, including delivery of cardioplegia for adequate myocardial preservation; grafting diffusely diseased coronary arteries; embolization of debris from atherosclerotic vein grafts that leads to myocardial infarction; lack of adequate conduits; and difficulties in performing the reoperative median sternotomy. As experience with repeat myocardial revascularization has increased, many technical advances have been made, including improved cardioplegia delivery and the use of internal mammary artery grafts [10, 11].

Despite these advances, however, the risk for this procedure is still much greater than that for primary isolated CABG. Lytle and associates [9], in an analysis of 1,500 coronary reoperations, suggested a fourfold increase in operative mortality. Our experience shows that almost 7% of our group 2 patients underwent repeat operation as opposed to 1.9% in the earlier group; this is similar to the experience reported by Naunheim and associates [1]. However, of the 16 patients in group 2 in our series who died, only 1 was undergoing a reoperative procedure.

Perhaps the most important trend in contemporary myocardial revascularization is the increased number of patients having isolated CABG on an emergency basis. This trend has been seen in many recent isolated CABG series, and up to a tenfold increase in operative mortality for patients undergoing emergency procedures has been demonstrated [1–3, 12]. Thirteen percent of our recent patients have had emergency operations as opposed to 3% previously.

Not only has the number of emergency procedures increased, but the type of emergency has changed as well. In recent years, acute intervention for evolving myocardial infarction has been employed on a more frequent basis. The increased use of the intraaortic balloon pump and rapid-access cardiopulmonary bypass circuits has led to more heroic operative attempts to salvage moribund patients. This is reflected in our series by the fact that of the 13 group 2 patients having emergency operation who died, 6 were in profound cardiogenic shock or cardiac arrest despite inotropic support and use of an intraaortic balloon pump preoperatively, and 2 had been placed on femorofemoral cardiopulmonary bypass in the cardiac catheterization laboratory because of intractable ventricular fibrillation. Only 2 patients undergoing an emergency operation for unstable or postinfarction angina died. Renal failure developed in 1 who died of an arrhythmia during dialysis on postoperative day 12. The second death occurred in a patient who sustained a massive pulmonary embolism seven days after repair of an abdominal aortic aneurysm and 17 days after isolated CABG. Three of the deaths in the emergency group occurred after PTCA.

Further evidence of the changing role of cardiac surgeons in the management of coronary artery disease is demonstrated by the expanding use of angioplasty. Since its introduction in 1977, there has been a progressive broadening of the indications for using PTCA and a tightening of indications for performing CABG. The result is that patients with more advanced disease undergo CABG as opposed to PTCA [7]. The expected major complication rate of angioplasty leading to emergency operation ranges between 3.7% and 13.1% [13–15]. Emergency surgical revascularization is possible with increased but acceptable risk in terms of operative mortality for both elective and emergency PTCA complications [16]. However, the incidence of myocardial damage is markedly increased in both these situations [17]. At our institution, 343 angioplasties were performed during the group 2 analysis period, and emergency CABG was required in 5% of the patients. All but 3 of these patients survived. However, the number of angioplasties performed for single-vessel and double-vessel coronary artery disease is likely to continue to grow, and thereby lead to a progressively worsening profile of patients undergoing isolated CABG. It is interesting to note that 36% of the patients having isolated CABG within 1 year of PTCA were found to have major triple-vessel coronary artery disease. Arcidi and colleagues [2] determined that 32% of the patients who had undergone isolated CABG in 1984 would have been offered PTCA in 1986.

In summary, the characteristics of patients seen for isolated CABG in recent years have changed. The present population of patients is older, contains more women, has more preoperative risk factors, and has worse preoperative symptoms than earlier patients. This change may be due to the expanded scope of operative candidacy prompted by technical surgical improvements and the diversion of lower-risk patients to nonoperative revascularization. Although these changes may have led to a slight increase in morbidity, operative mortality remains low. Surgical intervention in patients with evolving myocardial infarction as a complication of PTCA increases the operative risk.

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DISCUSSION

DR BRUCE W. LYTLE (Cleveland, OH): I congratulate Dr Davis and his colleagues on this careful analysis of their changing practice. If I can paraphrase their findings, their patients are getting older, are sicker, have more severe coronary artery disease, and include more women and patients undergoing reoperation and emergency operation. We are all sympathetic. These changes are occurring nationwide. But these trends are really only in part related to the advent of angioplasty and, in fact, are a continuation of trends that existed long before PTCA was ever developed.

The overall number of bypass operations has continued to increase, and the largest impact on our practices has not resulted from the subtraction of a good-risk population for PTCA, but rather from the fairly dramatic expansion of the number of patients undergoing bypass operation who fall into subgroups formerly considered to have a high surgical risk.

Several factors have contributed to this shifting of the patient population. One is patient acceptance. After 20 years, bypass surgery is now part of American culture. Almost all Americans know someone who has undergone successful CABG, and few patients are currently willing to accept the statement that "nothing can be done." In addition, the sicker they are, the less conservative they are willing to be.

A corollary is that patient aspirations have increased, particularly among the elderly. Patients in their 70s and 80s are just not willing to accept the limitation in activity level or life span associated with severe coronary artery disease. That philosophy accounts in part for the fairly dramatic expansion of the number of elderly patients who are undergoing coronary operations.

Physician confidence in the operation is high. Even the most conservative cardiologist now accepts the basic premise that CABG works.

We also have to consider the influence of the randomized studies. The shortcomings of the Veterans Administration Cooperative Study, the Coronary Artery Surgery Study, and the European Cooperative Study have been pointed out. Despite the shortcomings, however, all of these studies clearly showed that there were subsets of patients whose long-term survival was better if they were operated on than if they weren't. In general, the more extensive the coronary artery disease and the worse the left ventricular function, the more survival advantage was achieved with operation. These positive results of the randomized trials have clearly shifted the spectrum of bypass patients toward those with more extensive disease, a trend that is perfectly appropriate.

The emergence of interventional cardiology has had an impact not only because of PTCA but also because of thrombolysis. The availability of thrombolytic agents has increased the aggressiveness of many cardiologists dealing with acute ischemia syndromes, and in many institutions, the spin-off in terms of emergency operation has been substantial. In addition to siphoning off patients with single-vessel disease, angioplasty has created a new disease, the angioplasty shambles, characterized by an almost infinite variety of challenging emergency traumatic coronary pathologies, with which we're all becoming familiar. Finally, the surgical practice at a single institution will be strongly influenced by local factors, including the capability and mind-set of the surgical team and referral patterns.

The changes in the patient population are important. We all recognize that the composition of the patient population influences surgical risk, but there are also increasingly important economic factors. Dr Davis and his colleagues found that the length of hospital stay was longer for their more recent patients. We are in an era of fixed reimbursement, and older patients, sicker patients, and patients undergoing reoperation or emergency operation need more costly care. These are observations that we are going to have to continue to point out to the other players on the field of medical economics.

DR KEITH S. NAUNHEIM (St. Louis, MO): I congratulate the authors on their excellent presentation. These results are very similar to those my colleagues and I presented last year to The

Society. Unlike our review, however, in the present study there was no significant deterioration in left ventricular function over the interval studied. The mean ejection fraction in the studied patients remained level at about 57%, a percentage that indicates a very high number of normal ventricles. I wonder if the authors believe this stability in left ventricular function was partially responsible for the maintenance of a low operative mortality throughout the interval. Several similar studies have shown a gradual but persistent deterioration over time in the left ventricular function of the average operative candidate. Do the authors have an explanation for why function remained stable in their study?

I think it is essential for all cardiothoracic surgeons to recognize the relevance of this topic. Dr Lytle has already pointed out that there are major economic ramifications that result from the general decline in the clinical profile of patients undergoing cardiac procedures. It is also necessary that we recognize that these changes will have important consequences when dealing with governmental regulatory agencies. It must be made clear to such regulatory bodies that raw mortality data cannot be taken at face value but must be considered in light of appropriate risk stratification.

DR ANTHONY J. ACINAPURA (New York, NY): I also congratulate Dr Davis on his excellent presentation and the entire Hershey group on their superb results.

I agree that multiple factors have changed the demographics of coronary bypass patients. Percutaneous transluminal coronary angioplasty has taken care of the majority of low-risk patients, namely, the younger patient with less severe coronary artery disease and well-preserved left ventricular function. A substantial number of patients have undergone numerous repeat angioplasties and are seen with coronary artery disease that has progressed in severity; as a result, they may or may not have had one or more myocardial infarctions. Most important are the large number of younger patients with well-preserved ventricular function who have been siphoned off by angioplasty.

As a result, at St. Vincent's Hospital, the average age of our coronary bypass patients has reached 64 years. From 1981 through 1986, the number of patients 70 years of age or older has gradually increased. In 1987, 35% of our patients were 70 years of age or older, and as you would expect, these patients had more advanced coronary artery disease; triple-vessel disease in 90%; left main stenosis in 35%; unstable angina in 66%; and impaired ventricular function in 68%. The incidence of postoperative complications was significantly higher in this group of older patients, as was the operative mortality (8%), especially in women and especially in the subset of patients older than 70 years with unstable angina pectoris. Although cardiac failure was the cause of death in only 15% of the patients older than 70 years, the majority of these patients died late in their hospital course of complications such as prolonged ventilatory support, renal failure, cerebrovascular accidents, and eventual sepsis.

With the increasing number of patients 70 years of age or older undergoing coronary bypass operation, 35% of our patients in 1987, I think that mortality associated with elective coronary artery procedures will continue to increase. In 1987, the combined operative mortality was 4.3%. If we exclude the patients 70 years of age or older, it was only 1.8%.

As a result, I do not agree that the change in demographics will allow us to continue to have low operative mortality in coronary bypass patients, and I have two questions for Dr Davis. What percentage of your patients were 70 years of age or older, and what is your cutoff for operative mortality? Is it a 30-day period or is it condition at the time of discharge?

DR DAVIS: I thank the discussants very much for their interesting comments. In response to the question about the number of patients who were 70 years of age or older, in the recent group of patients, we know that 36% were older than 65 years and 17.2% were older than 70 years. This is in contrast to the earlier group of patients; 10.9% were older than 65 years and only 5.2% were 70 years of age or older.

In terms of reporting mortality, we used in-house operative mortality and 30-day mortality. Patients who died within 30 days of operation or in whom some complication developed that kept them in the hospital after the operation, prevented their discharge, and led ultimately to their death were included.

Although overall ventricular function was not seen to be worse in the more recent patients, preoperative ventricular function was significantly worse in the patients in that group who died. Of the 9 group 2 patients who died after an elective procedure, 4 had a preoperative cardiac index of less than 2 L/min/m^2, and 5 had an ejection fraction of less than 35%. Mortality after an elective procedure does not appear to have changed despite a worsening patient profile. This is probably due to improvements in surgical technique as well as postoperative intensive care.

One of our biggest concerns is the concept of quality assurance. It is of utmost importance that we avoid public misconception about raw mortality data and that we examine the data with an eye toward analysis of preoperative risk factors.

Repair of Truncus Arteriosus in the Neonate and Young Infant

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Louise B. Callow, RN, MSN, David J. Underhill, MD, Albert P. Rocchini, MD,
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Infants with truncus arteriosus present a difficult management issue. Because of the high operative mortality, repair is often delayed beyond the first 3 to 6 months of age. We reviewed our experience with 11 neonates and young infants with truncus arteriosus undergoing repair (median age, 21 days). Five patients also had major truncal valve insufficiency, and 2 required valve replacement. Right ventricle–pulmonary artery continuity was established with a porcine valved conduit in 3 patients and an aortic or pulmonary homograft in 8. There was 1 operative death (9%; 70% confidence limits, 3%–22%) and 1 late death over a mean follow-up of 21 months (range, 4 to 32 months). Eight of the 9 late survivors are growing normally. Echocardiographic examination revealed normal ventricular function in all patients (mean shortening fraction, 39%). Doppler assessment demonstrated trivial prosthetic or homograft valve regurgitation in 7 patients and mild to moderate obstruction in 5 patients. This recent experience with repair of truncus arteriosus indicates that the operative risk is low even in the neonate. Repair in the first month of life should be recommended before the development of critical congestive heart failure or irreversible pulmonary vascular disease.

(Ann Thorac Surg 1989;47:499–506)

Truncus arteriosus accounts for approximately 2% to 4% of all congenital cardiac malformations [1–3]. It is characterized by a single arterial trunk and semilunar valve leaving the heart [4, 5]. This vessel gives rise to the systemic, pulmonary, and coronary circulations. The severe hemodynamic burden imposed by the high flow and elevated pulmonary artery pressure leads to the development of congestive heart failure early in life. Low diastolic pressure due to runoff from the truncal artery into the low-resistance pulmonary circuit can result in decreased coronary perfusion and diminished ventricular performance. The presence of substantial truncal valve regurgitation further compounds the clinical picture. Without treatment, survival for more than 1 year is rare. Furthermore, the development of pulmonary vascular occlusive disease occurs early and can lead to a significantly increased operative risk or even inoperability by 3 to 6 months of age [6].

Following the landmark contribution of Ebert and colleagues [7], several reports [8, 9] have demonstrated improvement in the outcome of patients undergoing complete repair of truncus arteriosus. However, survival after repair in the first month of life remains uncommon, and some groups [8, 10, 11] continue to recommend postponing operation until the patient is 3 to 6 months of age.

At The University of Michigan, we have pioneered the surgical treatment of truncus arteriosus since the first successful repair was performed at this institution in 1962 [12]. Although early repair with a nonvalved conduit was initially preferred [13, 14], more recent experience has indicated that insertion of a valve in the pulmonary position may provide a substantial hemodynamic advantage in these generally very ill patients. Beginning in 1986 at The University of Michigan, all infants with truncus arteriosus have undergone complete repair with a valved conduit as soon as the patient is referred for initial diagnosis, regardless of age or size. Because the majority of these patients are seen soon after birth, most of our repairs have been performed in neonates. We, therefore, reviewed our entire recent experience with the surgical treatment of truncus arteriosus to assess the results of this practice.

Material and Methods

Between January 1986 and May 1988, a total of 13 patients with the diagnosis of truncus arteriosus were seen at C.S. Mott Children's Hospital of The University of Michigan. One 8-year-old boy underwent repair after pulmonary artery banding performed in infancy at another institution, and is excluded from further review. One neonate sustained a cardiac arrest during catheterization and died within a few hours before any surgical intervention. The remaining 11 patients underwent primary repair in infancy and form the basis of this report.

There were 4 male and 7 female infants (Table 1). Age ranged from 4 days to 4 months (median age, 21 days) with only 2 patients older than 3 months. Weight ranged from 1.9 to 4.1 kg (mean weight, 3.3 kg).

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Table 1. Clinical Characteristics of Patients With Truncus Arteriosus

Patient No.	Age	Weight (kg)	Sex	Associated Diagnoses	Outcome and Length of Follow-up
1	4 mo	3.8	F	Preoperative respiratory arrest, CNS damage, partial DiGeorge syndrome	CNS damage, no cardiac symptoms; 32 mo
2	4 days	2.8	F	None	Well; moderate CHF; 31 mo
3	2 mo	3.5	F	None	Well; 30 mo
4	3.7 mo	4.1	F	None	Well; 27 mo
5	21 days	3.5	F	Left SVC, absent right SVC, restrictive VSD	Operative death
6	28 days	1.9	F	None	Well; 19 mo
7	12 days	3.8	F	Nonconfluent pulmonary arteries	Well; 18 mo
8	13 days	3.4	M	None	Well; 14 mo
9	10 days	2.2	M	Partial DiGeorge syndrome	Late truncal valve replacement; 14 mo
10	21 days	3.4	M	Cleft lip and palate, DiGeorge syndrome	Late death
11	6 days	3.9	M	None	Well; 4 mo

CHF = congestive heart failure; CNS = central nervous system; SVC = superior vena cava; VSD = ventricular septal defect.

The clinical characteristics and associated diagnoses are also listed in Table 1. One patient (patient 1) sustained central nervous system damage when an endotracheal tube became dislodged during air transport prior to surgical repair. Three patients had either partial (2) or complete (1) DiGeorge syndrome. One patient (patient 5) had a restrictive ventricular septal defect and an absent right superior vena cava, and 1 (patient 7) had nonconfluent pulmonary arteries with the left pulmonary artery supplied by a ductus arteriosus. Preoperative diagnosis was established in each case by two-dimensional echocardiography/Doppler examination. Because of suspected associated lesions, preoperative cardiac catheterization was performed in 3 patients. Aortography only was performed in 1 patient to better quantify the degree of truncal valve regurgitation.

Using the classification of Collett and Edwards [15], 1 patient had type 1 anatomy and 5 patients had type 2 (Table 2). Four patients had an intermediate form between types 1 and 2 with both pulmonary arteries arising from the left posterior wall of the truncal vessel. The remaining patient had nonconfluent pulmonary arteries. The right pulmonary artery arose from the left posterolateral aspect of the truncal vessel, and the left pulmonary artery arose from the ductus arteriosus. The ventricular septal defect was a typical outlet defect in 9 patients. In 1, it extended

Table 2. Operative Details

Patient No.	Anatomical Classification	VSD Anatomy	Truncal Regurgitation	Associated Procedures
1	2	Perimembranous outlet	0	None
2	1	Outlet	3+	None
3	2	Outlet	0	None
4	2	Outlet	2+	None
5	1–2	Restrictive outlet	0	VSD enlargement
6	1–2	Outlet	0	None
7	1[a]	Outlet	4+[b]	TVR,[c] reconstruction of nonconfluent pulmonary arteries
8	2	Outlet	0	None
9	2	Outlet	3+	None
10	1–2	Outlet	0	None
11	1–2	Outlet	4+[b]	TVR

[a] The right pulmonary artery arose only from the truncal vessel. [b] This patient had truncal valve stenosis (36-mm Hg gradient). [c] Truncal valve replacement was performed ten days after repair.

TVR = truncal valve replacement; VSD = ventricular septal defect.

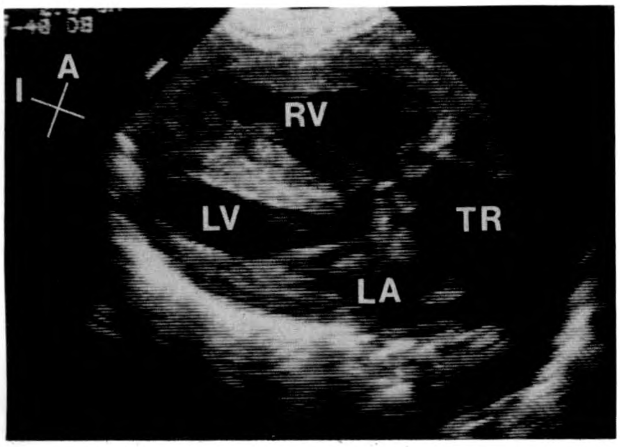


Fig 1. (Patient 7.) Parasternal long-axis view in an infant with truncus arteriosus. The truncal valve is thickened, rolled, and myxomatous. This still frame was taken during diastole and demonstrates a large regurgitant orifice. By Doppler examination, there was severe truncal valve regurgitation and a 36-mm Hg peak instantaneous pressure gradient across that valve. (A = *anterior;* I = *inferior;* LA = *left atrium;* LV = *left ventricle;* RV = *right ventricle;* TR = *truncus arteriosus.)*

Table 3. Right Ventricle/Pulmonary Artery Conduits

Patient No.	Size (mm)	Type
1	14	Carpentier-Edwards
2	12	Hancock
3	12	Hancock
4	13	Aortic homograft
5	13	Aortic homograft
6	8	Aortic homograft
7	10	Aortic homograft
8	14	Pulmonary homograft
9	11	Pulmonary homograft
10	14	Pulmonary homograft
11	14	Pulmonary homograft

to the tricuspid valve annulus (perimembranous), and in the remaining patient, the defect was moderately restrictive. Truncal valve regurgitation was absent in 6 patients, 2+ in 1 patient, 3+ in 2 patients, and 4+ in 2 patients. In these last 2 patients, the valves were quadricuspid with thickened, immobile leaflets that did not close in diastole (Fig 1). Both patients had systolic gradients of 36 mm Hg across the valve by Doppler examination; none of the other patients had evidence of outflow tract gradients.

Operative repair was performed using bicaval cannulation with low-flow cardiopulmonary bypass at systemic temperatures of 20°C. The pulmonary arteries were snared at the onset of bypass, and dilute blood cardioplegia (4°C) was delivered through the truncal vessel after placement of the cross-clamp. Cross-clamp times ranged from 45 to 95 minutes (mean time, 76 minutes). The pulmonary arteries were excised from within the truncal vessel after the bifurcation was exposed through a short, vertical anterior incision (Fig 2). This allowed accurate removal of the pulmonary bifurcation without injury to the truncal valve or left coronary artery. The resultant defect was closed with a patch in each instance to prevent distortion of the truncal valve.

Right ventricle–pulmonary artery continuity was established with a valved conduit in each patient (Table 3). In the first 3 patients in the series, a heterograft (14-mm Carpentier-Edwards in 1 patient, 12-mm Hancock in 2 patients) was implanted. Cryopreserved aortic homografts (CryoLife, Inc, Marietta, GA) were used in 4 patients. The last 4 patients received cryopreserved pulmonary homografts, which are currently preferred because of their thinner walls and greater ease of handling.

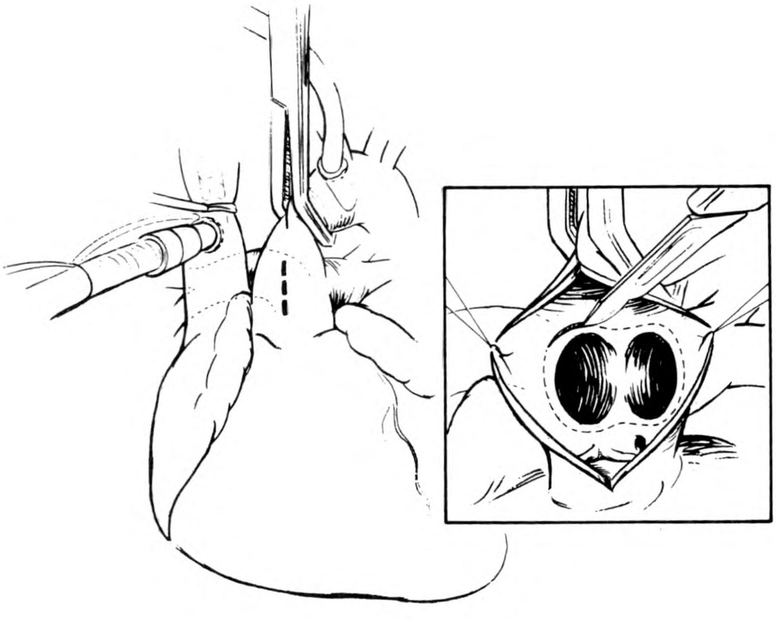


Fig 2. Initial step in the repair of truncus arteriosus. An incision is made in the anterior wall of the truncal vessel to allow accurate removal of the pulmonary artery bifurcation without damaging the valve or left coronary artery.

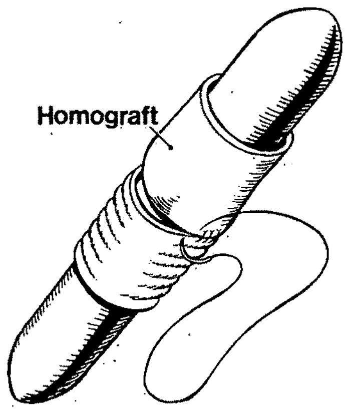


Fig 3. The cryopreserved homograft is stented over a dilator and extended proximally with a knitted Dacron conduit equal to or a few millimeters smaller than the diameter of the homograft.

Size selection was generally determined by homograft availability and patient size; the 8-mm aortic homograft was selected for the patient weighing only 1.9 kg. Despite the greater technical ease of implanting homografts than heterografts, "oversizing" was avoided. Homografts were extended proximally with knitted Dacron conduits equal to or one size smaller than the homograft (Fig 3). The Dacron extension was then sharply beveled so that only a 2- or 3-mm rim of Dacron remained posteriorly (Fig 4).

In the patient with nonconfluent pulmonary arteries (patient 7), the transected end of an aortic homograft was sutured to the divided left pulmonary artery in the hilum, and the right pulmonary artery was then connected to the side of the homograft (Fig 5). In the 2 patients who required truncal valve replacement, the vertical incision used to expose the pulmonary orifices was extended through the valve annulus into the ventricular septal defect. The ventricular septum was then divided further as described for aortoventriculoplasty to accommodate a large patch, which widened the annulus and permitted insertion of a 17-mm Omniscience disc prosthesis.

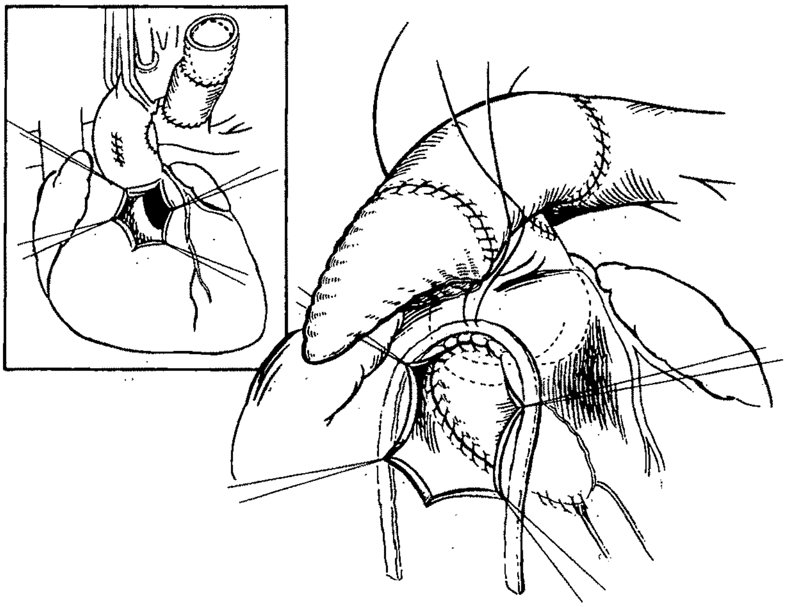
Truncal valve replacement was performed ten days after the initial repair in 1 patient (patient 7) because of severe regurgitation and congestive heart failure. This patient also had evidence of peripheral embolization presumed to originate from thrombus on the ventricular septal defect patch where it contacted the regurgitant jet (echocardiographic diagnosis), although no evidence of intracardiac thrombus was found at reoperation. Valve replacement was performed at the same time as the truncus repair in another patient (patient 11). In the presence of substantial untreated truncal valve regurgitation, the clamp was left in position longer, generally until systemic temperatures reached at least 32° to 35°C to allow immediate effective ventricular contractions to eject the regurgitant volume.

Results

There was 1 operative death (9%; 70% confidence limits, 3%–22%). The patient who died was a 3-week-old infant (patient 5) in whom ventricular fibrillation developed soon after induction of anesthesia. Multiple attempts at defibrillation were unsuccessful, and cardiopulmonary bypass was rapidly established. Although repair was completed uneventfully, the patient could not be weaned from bypass. One late death occurred 3 months after operation. The infant (patient 10) had DiGeorge syndrome and probable graft versus host disease, and was readmitted because of gastroenteritis and dehydration. An unrecognized perforation of the subclavian vein occurring during central venous line insertion caused the patient's death.

The remaining 9 patients have been followed for a mean of 21 months (range, 4 to 32 months). One patient (patient 9) required truncal valve replacement 6 months after

Fig 4. The homograft is attached to the pulmonary artery bifurcation distally. The proximal Dacron extension is beveled to leave only a short rim of Dacron posteriorly. The ventricular septal defect is closed in the standard fashion.



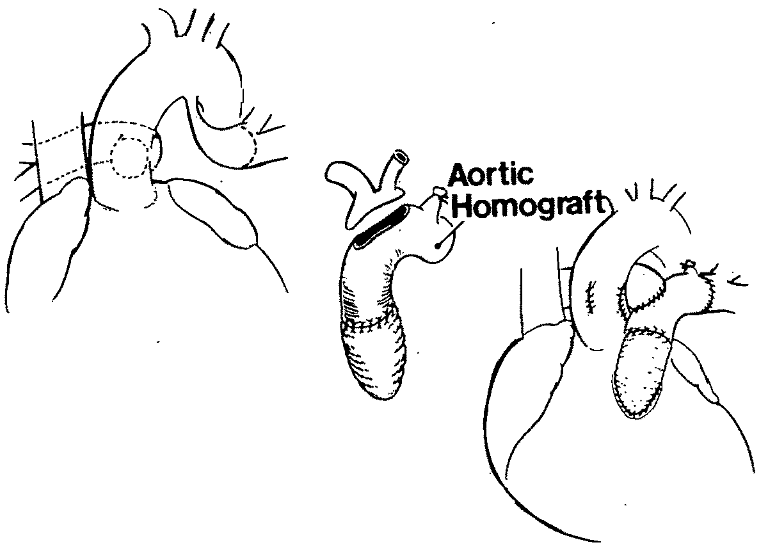


Fig 5. (Patient 7.) The repair in the patient with nonconfluent pulmonary arteries was accomplished by first attaching the divided left pulmonary artery to the distal end of a 10-mm aortic homograft. The mobilized right pulmonary artery was then implanted into the side of the homograft.

repair for persistent congestive heart failure and failure to thrive. No other patient has required reoperation to date. The 2 additional patients with substantial untreated truncal valve regurgitation (patients 2, 4) have continued to tolerate the regurgitation well and are growing, although 1 (patient 2) has moderate cardiomegaly and congestive heart failure. No patient has complete heart block.

Nine patients underwent detailed two-dimensional echocardiographic/Doppler studies 1 month to 29 months after repair (mean interval, 15 months). The findings are shown in Table 4. Left ventricular function was normal in each patient, with fractional shortening ranging from 29% to 56% (mean, 39%; normal, ≥28%). Truncal valve regurgitation was absent in 6 patients, trivial to mild in 1, and moderate in 2 patients. Conduit valve regurgitation was common (7/9), particularly in patients with homografts, but was never more than trivial in any patient. Doppler estimates of right ventricle–pulmonary artery peak instantaneous gradients ranged from 0 to 52 mm Hg. In the patient with a 52-mm Hg gradient, the majority of the obstruction was located at the origin of the left pulmonary artery (35 mm Hg) with an additional 17 mm Hg across the conduit itself.

Table 4. Two-Dimensional Echocardiography/Doppler Study at Follow-up

Patient No.	LV Fractional Shortening (%)	Truncal Valve Regurgitation	Conduit Valve Regurgitation	RV–PA Gradient (mm Hg)
1	36	0	0	0
2	34	2+	1+	29
3	34	0	1+	23
4	39	2+	1+	52[a]
6	43	0	1+	35
7	47	0	1+	14
8	29	1+	1+	0
10	56	0	0	0
11	36	0	1+	0

[a] This patient had a 17-mm Hg gradient across the conduit and an additional 35-mm Hg gradient across a stenosis at the origin of the left pulmonary artery.

LV = left ventricular; PA = pulmonary artery; RV = right ventricle.

Postoperative cardiac catheterization was performed in 2 patients. In 1 (patient 1), catheterization was done 12 months after operation and revealed normal pulmonary artery pressure and resistance. There was no truncal valve regurgitation or residual shunt. The other patient (patient 9) was studied elsewhere 5 months postoperatively because of persistent congestive heart failure believed secondary to severe truncal valve regurgitation. Truncal valve replacement was subsequently performed at another institution. An additional study was obtained after valve replacement because the infant could not be weaned from ventilator support. There was no residual shunt, truncal (prosthetic) valve regurgitation, or left ventricular dysfunction. Pulmonary artery pressure and resistance were normal. Ventilator dependency was thought to be secondary to phrenic nerve palsy. This patient was eventually weaned from the ventilator and discharged from the hospital. Neither patient had evidence of conduit stenosis at recatheterization.

Comment

It is now clear that infants with truncus arteriosus are best treated by early complete repair. Palliation with pulmonary artery banding offers no advantage and, even with modern surgical techniques, is unlikely to improve the mortality rates that can now be achieved with complete physiological repair. However, the exact timing of operation, particularly in neonates who have minimal or well-compensated congestive heart failure, remains in doubt. A number of authors [8, 10, 11, 16] continue to believe that the best results are obtained if repair is delayed beyond 2 to 3 months of age. It is important to note,

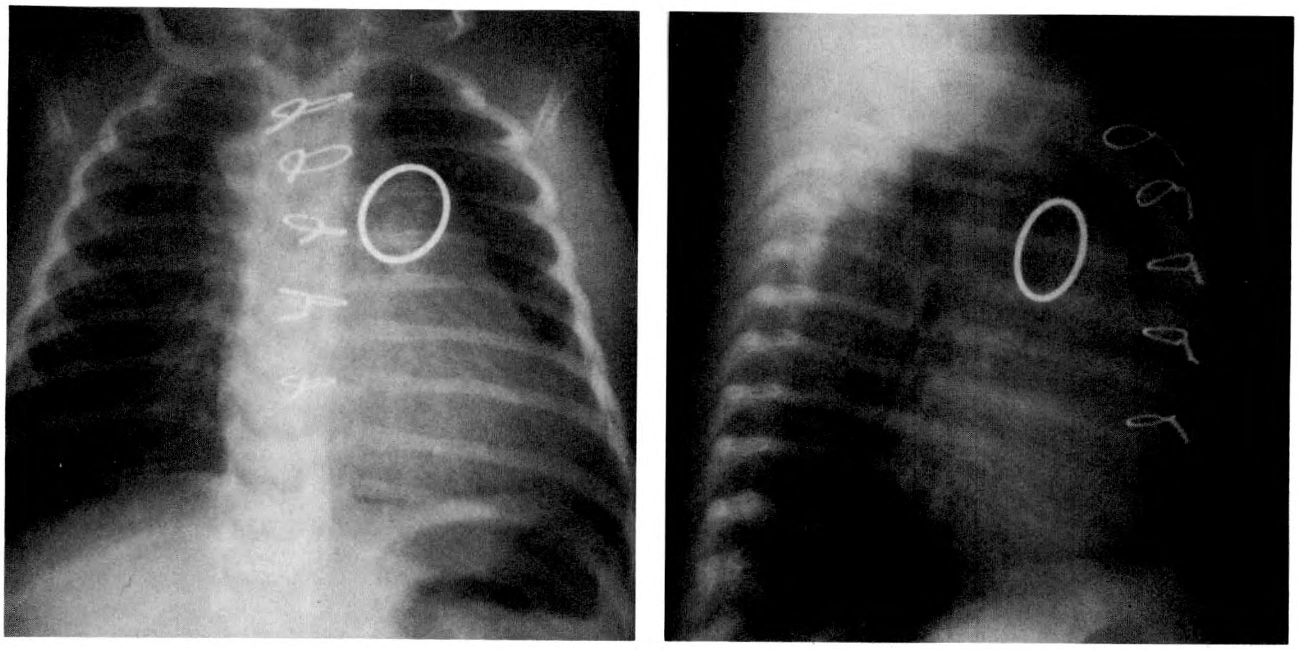


Fig 6. (Patient 2.) (A) Posteroanterior and (B) lateral chest roentgenograms made after repair with a 12-mm Hancock conduit. Proper positioning of the valve away from the sternum is demonstrated.

however, that medical treatment often gains very little and may further complicate the surgical risk if failure to thrive, infection, diminished ventricular function, or pulmonary vascular occlusive disease intervene.

For a number of years, it has been the practice at The University of Michigan to perform complete repair as early as possible for patients with truncus arteriosus. Although repair with a nonvalved conduit was advocated in the past because of the technical difficulties encountered when inserting valved porcine prostheses in small infants [13, 14], we now believe that the hemodynamic advantage of a valved conduit outweighs any potential disadvantages. With a few technical modifications, it is nearly always possible to place a 12-mm valved Dacron conduit even in tiny neonates (Fig 6). Furthermore, the current use of cryopreserved homografts offers a substantial technical improvement and the availability of conduits smaller than 12 mm if necessary.

This policy of early repair with valved conduits in all patients with truncus arteriosus has resulted in a unique experience of repair mostly in neonates. Although small in number, our series still allows some meaningful conclusions regarding complete repair in this potentially high-risk age group. Of the 11 patients, 8 were 4 weeks of age or less and 5 had moderate to severe truncal valve regurgitation. Two of these patients underwent successful truncal valve replacement at 22 days and 6 days of age. The former patient also required simultaneous repair of nonconfluent pulmonary arteries. Despite these factors, there was only 1 death (9%) in our series. The cause of death is not readily apparent, and no explanation could be found for the ventricular fibrillation that occurred before repair. The single late death was clearly noncardiac in cause, as this patient had an entirely uneventful recovery after operation and evidence of an excellent hemodynamic repair (see Table 4, patient 10).

Our method of repair differs little from previous reports from other centers. We prefer bicaval cannulation with low-flow cardiopulmonary bypass at 20°C. This has been possible in all patients, including the infant weighing 1.9 kg. A single dose of dilute blood cardioplegia is delivered, as this provides additional protection during the period of aortic cross-clamping [17, 18]. No special precautions are taken in patients with major truncal valve regurgitation when replacement is not planned except to assure prompt initiation of cardiac action on reperfusion to eject the regurgitation volume of blood reaching the left ventricle. Truncal valve replacement should be performed at the time of complete repair when the valve is severely regurgitant, particularly if stenosis is also present, regardless of patient age or size. In our experience, attempts to postpone valve replacement in this setting have been unsuccessful. Division of the truncal valve annulus with patch enlargement of the valve ring as described for aortoventriculoplasty was readily accomplished in 2 patients and allowed insertion of a relatively large disc prosthesis. Possibly, insertion of an aortic homograft, either freehand or as an extended root replacement, may offer a substantial advantage over a mechanical valve [19]. However, the longevity of homografts in the aortic position in the neonate remains unknown.

Use of fresh and cryopreserved homografts to provide right ventricle–pulmonary artery continuity is a more tested procedure with great advantages over Dacron conduits containing porcine valves [20, 21]. Avoidance of rigid prostheses and a greater technical ease of suturing with improved hemostasis are extremely desirable, particularly in neonates. Although mild regurgitation is common, in none of our patients has this been hemodynamically significant. Long-term durability is limited by valve calcification and neointimal proliferation, particularly when woven Dacron is used to lengthen the homograft [22]. Our use of knitted materials with little posterior rim to minimize the circumferential amount of Dacron may improve longevity. The residual gradients found in the homograft group (see Table 4) were thought to be secondary to the small size of the conduits themselves and, in one instance, to stenosis of a branch of the left pulmonary artery. No evidence of isolated proximal narrowing at the Dacron extension was found.

In conclusion, this experience supports the notion that complete repair of truncus arteriosus should be performed as early as possible after diagnosis. Optimally, this would occur within the first month of life, regardless of symptoms. When the diagnosis is made at birth or even in utero and the neonatal pulmonary vascular resistance remains elevated, postponing repair for a few weeks to allow resistance to fall is beneficial. Cardiac catheterization may not be necessary if two-dimensional echocardiography/Doppler examination can identify both pulmonary arteries, demonstrate the anatomy of the aortic arch, and define the function of the truncal valve. It might also be necessary if specific quantification of pulmonary vascular resistance is required. Truncal valve replacement should be performed when severe regurgitation is present, especially when associated with truncal valve stenosis. The truncal valve should be left alone when regurgitation is less than severe. Right ventricle–pulmonary artery continuity is best established with a cryopreserved pulmonary or aortic homograft, although porcine heterograft conduits remain a satisfactory alternative [23]. This practice has resulted in an acceptable operative mortality (9%) despite the high percentage of neonates and the complexity of associated lesions.

Addendum

Since the final preparation of this manuscript, 2 additional neonates have undergone successful repair of truncus arteriosus, both at 1 day of age. One patient also required replacement of the truncal valve because of severe insufficiency.

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DISCUSSION

DR KEVIN TURLEY (San Francisco, CA): I thank The Society for the privilege of discussing this paper and the authors for forwarding authors for the excellent results in this series of difficult patients.

At the University of California, San Francisco, from 1975 through 1988, 217 patients less than 6 months of age underwent operation. The time frame for operation, that is, our recommended age for optimal elective repair, has decreased during that period from less than 6 months prior to 1980 to less than 3 months through 1984 to less than 6 weeks in the current era.

The reason we thought operation was difficult in infants less than 6 weeks or a month old was the mismatch that we often see between a heterograft conduit (the smallest available being a 12-mm conduit) and the right ventricle of these small infants. The use of allografts has changed this situation substantially, and early repair in the first month of life is both feasible and desirable.

In reviewing our heterograft series, we have found that obstructions occurred in the Dacron conduits at multiple levels, with pseudointimal formation, valve degeneration, and involvement of the proximal conduit in the obstructing process.

In one instance, dissection of the pseudointima of the proximal conduit resulted in obstruction. For this reason, our allografts are placed with the muscle ridge posteriorly, leaving the mitral leaflet to form part of the arterial patch. A Teflon felt bolster is placed posteriorly, the suture is taken down the ventricular muscle, about one third of the way through the ventricular septal defect patch, and then back and up through the muscle, placing this muscle within the ventricular cavity. The mitral valve is then augmented with a piece of pericardium or allograft arch tissue, placing the allograft valve perpendicular to the ventricular wall, thereby eliminating major valvular regurgitation while avoiding the need for any Dacron extension with the obstructive consequences.

I ask the authors, first, about this concern of the placement of the circumferential Dacron graft proximal to the allograft. Second, I ask that they expound on the case of graft versus host reaction 3 months postoperatively in the patient with DiGeorge syndrome. We have not encountered this problem, and it is one of great concern. Finally, it is stated in the manuscript that the authors would operate in early infancy when the patient is first seen. We see a number of patients with pulmonary hypertension in the first week of life. Would the authors operate at that point or wait for the development of congestive heart failure and high flow to initiate an operative approach?

DR BOVE: I thank Dr Turley for his comments.

I will reply to his questions beginning with the Dacron extension. We, too, have had concerns about the use of Dacron to extend these conduits. We prefer the pulmonary homograft over the aortic homograft, which, of course, does not give us the option of using the anterior leaflet of the mitral valve to extend it over the ventriculotomy. What we have utilized, not only in the patients with truncus but in all of our patients who have had homografts, are proximal extensions of the conduit with knitted Dacron baked in the autoclave either with autologous blood or albumin. We have not had hemorrhage problems with that method, although it remains to be seen if the use of knitted material versus woven material will decrease the incidence of peel formation and late obstruction.

Regarding the case of graft versus host disease in the 1 infant with DiGeorge syndrome, I have to say that the diagnosis was never firmly established. The infant was admitted to the cardiology service and died as a result of the mishap with central venous line placement before the diagnosis was established. But it was suspected by the admitting cardiologist in view of the infant's other syndrome.

Dr Turley's point about waiting until the infant goes into congestive failure is a good one, and I concur. I do not see any real need to operate on these infants immediately if they are not in congestive heart failure; rather, I would wait until congestive heart failure begins to be seen, which in our experience does not generally take very long. But if we see an infant who is 1 or 2 days of age and is not in congestive failure, we would probably wait a week or so. Most infants seen with severe failure at that age, however, do have important truncal valve regurgitation. In fact, we have seen an inordinately high percentage of that in our patients, and it really complicates the surgical management.

Comparison of Coronary Artery Bypass Grafting and Percutaneous Transluminal Coronary Angioplasty as Initial Treatment Strategies

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Early and late results of primary nonemergency coronary artery bypass grafting in 1,000 consecutive patients and primary nonemergency percutaneous transluminal coronary angioplasty performed concurrently in 389 patients were retrospectively compared. The coronary bypass population was significantly older and more symptomatic and had more prior myocardial infarctions, more left main and multiple-vessel coronary artery disease, and poorer ventricular function. Hospital mortality rates for coronary bypass grafting and angioplasty were 0.4% and 0.5%, respectively, and infarction rates were 1.7% and 5.1%, respectively ($p < 0.01$). Including hospital events for the coronary bypass and angioplasty populations, actuarial survival at 5 years was 92.3% versus 96.3% ($p = 0.04$), freedom from myocardial infarction was 94.6% versus 88.1% ($p < 0.001$), freedom from subsequent angioplasty was 99.5% versus 75.2% ($p < 0.001$), freedom from subsequent coronary bypass grafting was 98.8% versus 84.9% ($p < 0.001$), and freedom from all morbidity and mortality was 87.1% versus 66.0% ($p < 0.001$), respectively. By Cox regression analysis for all 1,389 patients, only diminished ejection fraction and advanced age predicted poor long-term survival ($p < 0.001$). The only significant predictor of nonfatal late events was having had coronary angioplasty.

(Ann Thorac Surg 1989;47:507–16)

Since the development of percutaneous transluminal coronary angioplasty by Gruentzig [1] in 1977, this technique has rapidly developed and come to be considered either as a primary adjunct to the medical management of patients with ischemic heart disease or as a preferred alternative to coronary artery bypass grafting. The medical literature is replete with reports of the early success rates for this procedure when applied to large populations of patients with atherosclerotic coronary artery disease [2–5]. Although the procedure has been in use for more than a decade, very few reports document its midterm or long-term effectiveness [6–8]. Furthermore, few long-term comparisons of the results of percutaneous transluminal coronary angioplasty with those of synchronously performed coronary artery bypass grafting from the same institution have been made [9, 10], and we are aware of no reports of long-term follow-up of patients prospectively randomized to the two procedures from an institution.

In the absence of long-term comparative data, we decided to retrospectively review our experience with coronary artery bypass grafting and percutaneous transluminal coronary angioplasty as initial invasive treatment strategies for patients with ischemic heart disease. To expand our ability to differentiate the results of the two procedures, we chose to look not only at the early success rates, but also the effectiveness of both procedures in providing patients with event-free long-term survival [11]. Finally, we investigated our patient population with ischemic heart disease treated by either of these procedures to determine the variables that predict long-term survival and nonfatal late events.

Material and Methods

Patient Population

The first percutaneous transluminal coronary angioplasty procedure performed at Massachusetts General Hospital was in July 1978. To eliminate the bias of including patients having angioplasty during the "learning curve" of the procedure at our institution, patient populations selected for this study came from a period beginning in early 1981. A base number of 1,000 patients having coronary artery bypass grafting was selected to provide an adequate sample size against which to compare all of the patients having percutaneous transluminal coronary angioplasty during the same period.

From March 1981 through May 1986, 1,236 consecutive patients had isolated coronary artery bypass grafting by one of us (C.W.A.) at Massachusetts General Hospital. During the same period, 550 consecutive patients had percutaneous transluminal coronary angioplasty performed in the cardiac catheterization laboratories of Massachusetts General Hospital.

Exclusion criteria used to censor patients from either group were an emergency procedure or prior percutaneous angioplasty or coronary artery bypass grafting. In

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Table 1. Patients Admitted to Study by Calendar Year

Year	CABG	PTCA
1981[a]	176	34
1982	196	39
1983	209	59
1984	194	72
1985	154	113
1986[b]	71	72

[a] The beginning month was March 1981. [b] The last month was May 1986.

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

addition, patients from the angioplasty subgroup were censored if no dilating catheters were actually inserted or if they would not have been a candidate for bypass grafting. Patients were censored from the coronary bypass cohort if the bypass grafting procedure was performed without the use of cardiopulmonary bypass.

Thus, during that period, 236 patients having coronary artery bypass grafting were excluded from the study because (1) the operative procedures were performed on an emergency basis (165 patients), (2) they had had a prior coronary artery bypass grafting or percutaneous angioplasty procedure (61 patients), or (3) the coronary grafting was done without the use of cardiopulmonary bypass (10 patients). During the same period, 161 patients taken to the catheterization laboratory for percutaneous transluminal coronary angioplasty were excluded from the evaluation because (1) the angioplasty procedure was done on an emergency basis (96 patients), (2) they had had a prior percutaneous angioplasty or coronary bypass grafting procedure (52 patients), (3) the screening catheterization done before the initiation of angioplasty revealed that the lesion was no longer amenable to angioplasty and therefore no dilating catheters were actually inserted (11 patients), or (4) the patient would not have been a surgical candidate for other medical reasons (2 patients).

The number of patients admitted to the study in each cohort by calendar year is recorded in Table 1. Although the distribution of coronary bypass patients by calendar year is generally constant, more than half of the angioplasty patients underwent the procedure during the last 18 months of this 5-year study.

The hospital records of the remaining 1,000 coronary bypass patients and 389 angioplasty patients were retrospectively reviewed by one of us (D.L.C.), a trained research nurse, for demographic data, risk factors, catheterization findings, operative or procedural characteristics, and results of the procedure. In particular, serial electrocardiograms and serum cardiac enzyme determinations were reviewed for each coronary bypass patient for the first three postoperative days. When similar information was available for the percutaneous transluminal coronary angioplasty patients, this was also recorded. A myocardial infarction was defined as either new Q waves on the electrocardiogram or elevation of the myocardial fraction of creatine kinase to more than 40 IU.

Follow-up

Follow-up information was collected as of October 1, 1985. Clinical information about survival and subsequent cardiac-related events was obtained by direct communication with the patients by trained personnel. If subsequent hospitalization, death, or cardiac-related events had occurred, the patient's physician or the appropriate hospital record department was contacted to document the events and details of any hospitalizations. Of the 1,389 patients, 2 could not be contacted for the follow-up study, 1 each from the coronary bypass and angioplasty populations. Thus follow-up was 99.9% complete. The mean follow-up was 3.0 years for the coronary bypass patients and 2.2 years for the angioplasty patients ($p < 0.01$).

Statistical Analysis

Clinical, angiographic, and operative differences between the two groups were tested for statistical significance by t test and χ^2 tests as appropriate. To expand the long-term evaluation of these two procedures, we chose to identify subsequent cardiac-related events that were easily quantified and that provided a reasonable estimate of major morbidity and mortality after each of these procedures: death, nonfatal myocardial infarction, subsequent percutaneous transluminal coronary angioplasty, or reoperative myocardial revascularization.

To describe the long-term results and to compare the results achieved by the coronary bypass and angioplasty groups, two types of event-free analysis were used: univariate actuarial (life-table) analysis [12] and multiple regression (Cox) survival analysis [13].

Two types of outcome (dependent) events were analyzed: simple and compound. The simple events were (1) death, (2) myocardial infarction, (3) coronary bypass grafting, and (4) percutaneous transluminal coronary angioplasty. The compound events were (1) any nonfatal event (morbidity) and (2) any event (mortality or morbidity).

Event-free analysis for each simple and compound event was done twice: once for events occurring at any time after the initial procedure and once for late (after hospital discharge) events only.

Several preoperative variables reported to influence long-term survival were evaluated as potential risk factors [14]: age, sex, type of angina (stable or unstable), New York Heart Association functional class, prior myocardial infarction, number of diseased vessels, presence of left main coronary artery disease, left ventricular end-diastolic pressure, and left ventricular ejection fraction.

For the univariate analysis, the values of age, ejection fraction, and end-diastolic pressure were combined to produce dichotomous variables. Life tables were compared using a χ^2 statistic [15] produced by the method of Lee and Desu [16]. No adjustments for multiple comparisons were made to the nominal p values. For the Cox regression analyses, the preoperative variables were included as independent variables along with "treatment group" (ie, initial treatment of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), and a stepwise procedure was used in which the criterion for a variable to be added to the model was a maximum partial likelihood ratio test corresponding to a

Table 2. Demographic, Clinical, and Catheterization Characteristics of the Two Study Groups[a]

	Patient Group		
Characteristic	Coronary Bypass (n = 1,000)	Percutaneous Angioplasty (n = 389)	*p* Value
Mean age (yr)	59.3	55.3	<0.001
Sex			
Male	850 (85)	278 (72)	<0.001
Female	150 (15)	111 (28)	
Angina pattern			
Stable	803 (80)	235 (60)	<0.001
Unstable	197 (20)	154 (40)	
NYHA functional class			
I	28 (3)	31 (8)	<0.001
II	215 (22)	140 (36)	
III	590 (59)	131 (34)	
IV	167 (17)	87 (22)	
Mean	2.9	2.5	<0.001
Congestive heart failure	56 (6)	9 (3)	0.02
Prior myocardial infarction	533 (53)	141 (36)	<0.001
Extent of disease			
One vessel	36 (4)	231 (60)	<0.001
Two vessels	217 (22)	134 (35)	
Three vessels	747 (75)	22 (6)	
Left main disease	210 (21)	5 (1)	<0.001
Mean left ventricular ejection fraction	0.59	0.65	<0.001
Mean left ventricular end-diastolic pressure (mm Hg)	15.4	14.3	0.05

[a] Numbers in parentheses are percentages.

NYHA = New York Heart Association.

probability of 0.10; a probability of 0.15 was the criterion for a variable to be removed from the model [17].

Results

The distribution of important demographic, clinical, and catheterization findings for the two patient groups is shown in Table 2.

Bypass Grafting

All of the 1,000 coronary artery bypass patients underwent bypass grafting with hypothermic fibrillatory arrest without aortic occlusion for myocardial preservation. The detailed aspects of the operative technique have been previously described [11, 18]. For the 1,000 patients, the average number of grafts per patient was 4.2. Eighty-eight patients, all in the later part of the study, received at least one internal mammary artery graft. The median length of postoperative stay was ten days.

Angioplasty

For the 389 patients having percutaneous transluminal coronary angioplasty, the procedure was performed using a variety of angioplasty catheters, the majority of which were inserted over a preliminarily placed guidewire. Angioplasty of an isolated lesion in one vessel was performed in 348 patients. Angioplasty of multiple lesions in a single vessel was performed in 29 patients and of isolated lesions in two coronary vessels in 12 patients. Angioplasty was judged successful according to previously described criteria [6]. The angioplasty procedure was considered successful in 83% of the 389 patients. In 66 patients, it was judged to be unsuccessful; in 39 (10.0%) because of an inability to cross the lesion, in 15 (3.8%) because of the occurrence of acute closure due to thrombosis of the treated vessel, and in 12 (3.1%) because of dissection of the vessel. The median hospital stay after the procedure was two days.

Table 3. Incidence of Hospital Morbidity and Mortality

Event	CABG	PTCA	*p* Value
Death	0.4	0.5	NS
Myocardial infarction	1.7	5.1	<0.001
Repeat PTCA	0	1.8	<0.001
Repeat CABG	0	6.9	<0.001
All events	1.9	9.2	<0.001

CABG = coronary artery bypass grafting; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

In-hospital Events

The incidence of in-hospital cardiac-related events for the two groups is reported in Table 3. Although there was no significant difference between the hospital mortality (ie, any death occurring during the hospitalization for the initial procedure or within 30 days of the procedure for those discharged from the hospital before that time) for the two groups, a significantly greater incidence of periprocedural myocardial infarction, subsequent percutaneous transluminal coronary angioplasty, subsequent coronary artery bypass grafting, and all combined morbidity and mortality was noted for the angioplasty patients compared with the coronary bypass patients.

Late Events

Five-year actuarial event-free rates for the coronary artery bypass and percutaneous angioplasty populations *including* hospital events are recorded in Table 4 and displayed

Table 4. Five-Year Actuarial Event-Free Rates Including Hospital Events

Event	CABG	PTCA	*p* Value
Death	92.3 ± 1.2	96.3 ± 2.2	0.04
Myocardial infarction	94.7 ± 1.1	88.1 ± 2.5	<0.001
Repeat PTCA	99.5 ± 0.3	75.2 ± 4.3	<0.001
Repeat CABG	98.8 ± 0.7	85.0 ± 2.0	<0.001
All events	87.1 ± 1.5	66.0 ± 4.8	<0.001

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

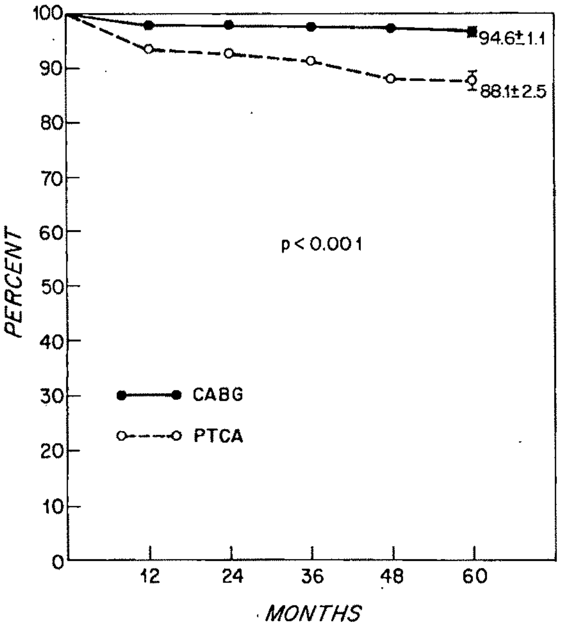

Fig 1. Actuarial freedom from myocardial infarction including hospital events. (CABG = *coronary artery bypass grafting;* PTCA = *percutaneous transluminal coronary angioplasty.)*

graphically in Figures 1 through 5. A significantly greater freedom from subsequent myocardial infarction, subsequent percutaneous transluminal coronary angioplasty, subsequent coronary artery bypass grafting, and all combined morbidity and mortality was noted for the coronary bypass patients compared with the angioplasty patients. Five-year actuarial survival for the angioplasty patients was 96.3% compared with 92.3% for the coronary bypass patients ($p = 0.04$).

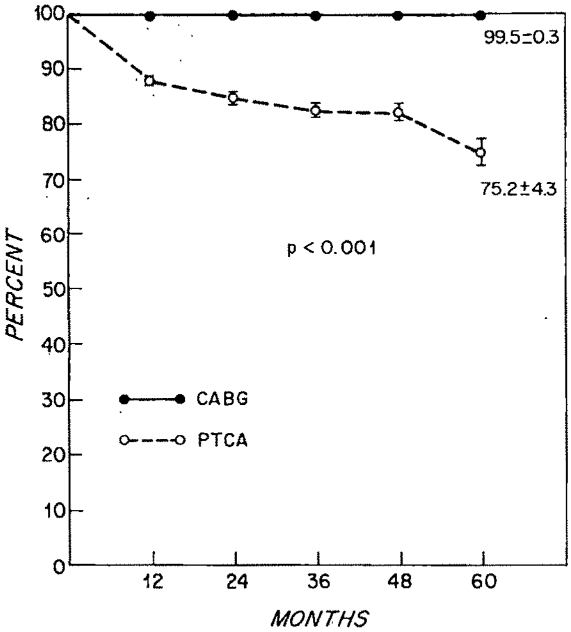

Fig 2. Actuarial freedom from subsequent percutaneous transluminal coronary angioplasty (PTCA) *including hospital events.* (CABG = *coronary artery bypass grafting.)*

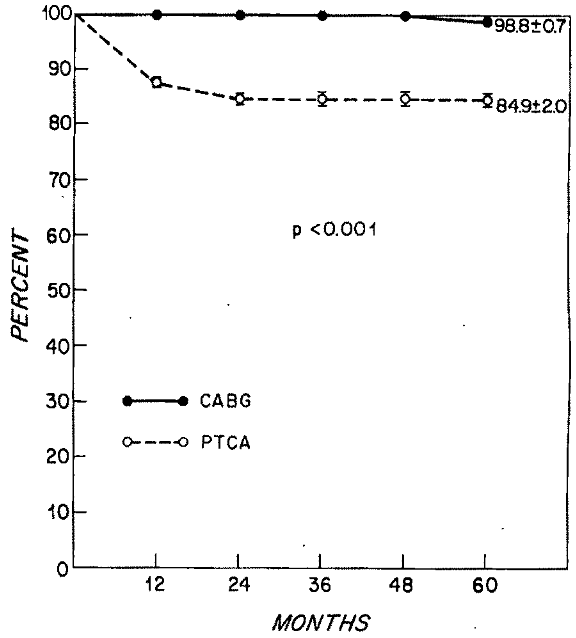

Fig 3. Actuarial freedom from subsequent coronary artery bypass grafting (CABG) *including hospital events.* (PTCA = *percutaneous transluminal coronary angioplasty.)*

The five-year actuarial event-free rates for the coronary bypass and angioplasty populations *excluding* hospital events are recorded in Table 5. Once again the coronary bypass patients had a significantly greater actuarial freedom from myocardial infarction, subsequent percutaneous transluminal coronary angioplasty, subsequent coronary artery bypass grafting, and all combined morbidity and mortality than the angioplasty patients. Five-year actuarial survival for the angioplasty patients was 96.8%

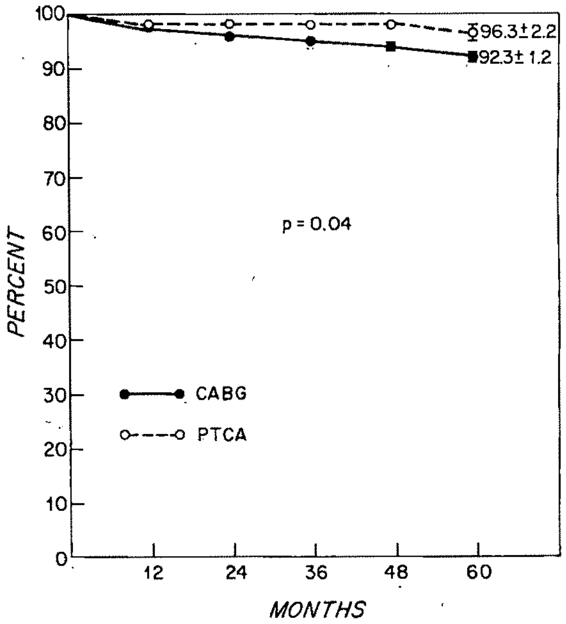

Fig 4. Actuarial survival including hospital events. (CABG = *coronary artery bypass grafting;* PTCA = *percutaneous transluminal coronary angioplasty.)*

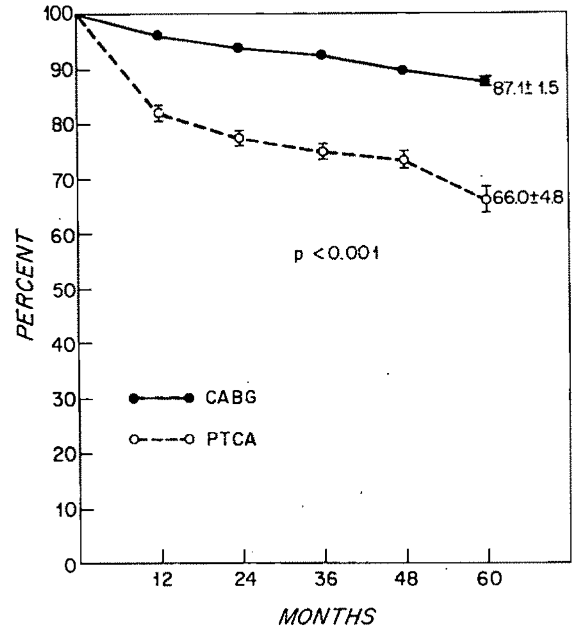

Fig 5. Actuarial freedom from all morbidity and mortality including hospital events. (CABG = *coronary artery bypass grafting;* PTCA = *percutaneous transluminal coronary angioplasty.)*

compared with 92.7% for the coronary bypass patients ($p = 0.02$).

Predictors of Survival and Nonfatal Events

Although univariate event-free analysis for all events except survival favored the coronary bypass cohort, actuarial survival favored the angioplasty group. However, univariate actuarial analysis of survival according to the preoperative variables showed that New York Heart Association functional class, age, number of diseased vessels, ejection fraction, and end-diastolic pressure affected survival. The coronary bypass population had less favorable distributions of all these risk factors than the angioplasty cohort.

Thus, the stepwise Cox regression analysis was performed. These covariates were used as risk factors plus the variable of treatment group (ie, original procedure = coronary artery bypass grafting or percutaneous transluminal coronary angioplasty). Age entered the model first, after which the p value for treatment group increased to 0.35. Ejection fraction entered next, after which all the remaining factors had a p value of less than 0.10 including treatment group with a p value equal to 0.53 (Table 6).

Table 5. Five-Year Actuarial Event-Free Rates Excluding Hospital Events

Event	CABG	PTCA	p Value
Death	92.7 ± 1.2	96.8 ± 2.2	0.02
Myocardial infarction	96.4 ± 1.0	93.2 ± 2.2	0.02
Repeat PTCA	99.5 ± 0.3	76.6 ± 4.3	<0.001
Repeat CABG	98.8 ± 0.7	91.9 ± 1.6	<0.001
All events	88.9 ± 1.6	74.2 ± 5.3	<0.001

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

Table 6. Factors Influencing Survival Following CABG or PTCA by Cox Analysis

Factor	p Value
Ejection fraction	<0.001
Age	<0.001
NYHA functional class	NS
No. of diseased vessels	NS
Treatment group	NS
Left ventricular end-diastolic pressure	NS

CABG = coronary artery bypass grafting; NS = not significant; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.

A second Cox regression analysis of survival was performed, this time limited to the two factors found significant (ie, age and ejection fraction) plus treatment group. Again, age and ejection fraction were the only significant factors, and the p value for treatment group was 0.56. (These adjusted survival differences according to group are not significant, but they are in favor of coronary artery bypass grafting, slightly reversing the survival pattern seen in the univariate analysis.)

By Cox regression analysis of subsequent angioplasty, subsequent coronary bypass grafting, combined nonfatal events, and total morbidity and mortality, treatment group was the only significant independent variable, and it was in favor of coronary bypass grafting. No other variables predicted nonfatal late events. There were no significant predictors of myocardial infarction.

Comment

During the early historical experience with coronary artery bypass grafting, numerous investigators decried the absence of properly designed prospective randomized trials of coronary artery bypass grafting and medical therapy for coronary artery disease [19, 20]. Subsequently, three large randomized series [21–23] were initiated whose results remain a source of contention to this day. Even in light of this history, cardiologists and cardiac surgeons failed to heed the warnings and develop prospective randomized trials of bypass grafting and angioplasty when percutaneous transluminal coronary angioplasty became an established approach for patients with coronary artery disease [24].

Recently, prospective comparisons between angioplasty and coronary bypass grafting for symptomatic patients with multiple-vessel coronary artery disease have been initiated at Emory University and by the National Heart, Lung, and Blood Institute. The results of these trials, however, will not be available for at least 5 to 10 years. In addition, the rapidly changing technology of coronary artery bypass surgery and particularly transluminal coronary angioplasty makes the application of the long-term results of such trials of questionable merit to future populations of patients for whom newer techniques will be available. Thus, although a retrospective observational study has obvious inherent limitations, it is, at present, the most practical approach for evaluating our current experience with the two procedures.

A properly designed prospective randomized comparison of two procedures used to treat patients with the same disease process is generally accepted as the best method for achieving a statistically valid comparison of the two procedures. The limitations of our retrospective observational study are obvious, including the possible exclusion of variables not measured that might have substantially influenced the stated results. Because both coronary bypass grafting and coronary angioplasty can be performed with quite low mortality rates and generally good late survival, comparison of the two procedures is difficult because of the small number of deaths in even large populations of patients. Thus we have chosen to supplement actuarial survival rates with the incidence of other easily definable cardiac-related events [11].

Acknowledging the important, inherent limitations of this study and after carefully delineating the significant demographic, clinical, and angiographic differences between these two patient cohorts, we chose to evaluate our results in three ways. First, as a simple initial determination of the relative risks of the two procedures, we have reported the in-hospital event rates. These results demonstrate that the risk of hospital death is similar for these two procedures despite their varying complexity. The reason why percutaneous angioplasty, a straightforward catheterization technique, should have a hospital mortality essentially identical to that of the more complex coronary artery bypass grafting is not clear.

Two factors may in part explain this unexpected result. First, coronary artery bypass grafting is uniformly directed at complete revascularization, whereas percutaneous transluminal coronary angioplasty is often utilized for only the more severe of several coronary lesions and may not completely relieve all stenoses that are dilated. Second, the procedure of coronary grafting is performed in such a way that minimal trauma is done to the artery being bypassed, and the area of disease is usually carefully avoided. In contrast, coronary angioplasty has as its basic principle the mechanical disruption of the artery wall [25]. Cardiac surgeons and angioplasty cardiologists are generally the beneficiaries of the forgiving nature of the coronary arteries to local trauma, but the disruption of angioplasty is an uncontrollable phenomenon. Also, the technique of coronary artery bypass grafting employs methods to mechanically support the circulation, thus providing time for mechanical and pharmacological adjustments should untoward events occur. Percutaneous angioplasty is performed without the support mechanisms that have made coronary bypass procedures possible. These factors might also account for the fact that the risk of nonfatal hospital events is significantly in favor of coronary artery bypass grafting versus percutaneous transluminal coronary angioplasty.

The second statistical method used to evaluate the two procedures was determining the incidence of death and nonfatal late events during follow-up and reporting these as actuarial event-free rates. The statistical methods used to compare these actuarial curves assess the shape of the curve over time as well as the final end points. Looking at both methods of comparing the actuarial event-free rates, namely, with and without hospital events, the coronary bypass population has a highly significantly greater freedom from subsequent myocardial infarction, subsequent percutaneous transluminal coronary angioplasty, subsequent coronary artery bypass grafting, and all combined morbidity and mortality compared with the coronary angioplasty patients. On the other hand, actuarial survival for the percutaneous transluminal coronary angioplasty patients was significantly greater than that for the coronary bypass population. However, our two patient populations have important significant differences in preoperative clinical characteristics and angiographic findings. The coronary bypass patients were significantly older, were more symptomatic, had had more prior myocardial infarctions, had a greater degree of left main and multiple-vessel coronary artery disease, and had poorer ventricular function. These highly significant differences would seem to make comparison of the long-term effectiveness of these two procedures statistically untenable. We therefore chose to evaluate the differences in long-term event-free rates according to procedural variables known to affect long-term survival and late cardiac-related events.

Thus, the third method of comparison of the two groups was accomplished with the use of the Cox stepwise logistic regression analysis model, which is specifically designed to account for the differences in the patient populations. In addition, with the use of this model, one can include procedure performed as a variable for evaluation. A similar approach was used by Loop and colleagues [14] to determine the relative impact of mammary artery and saphenous vein grafting on late cardiac-related events in quite disparate cohorts of patients. With the use of this statistical model and examining the entire 1,389 patients as a whole, only two factors were found to significantly predict poor long-term survival: diminished ejection fraction and advanced age. Indeed, when one accounts for these two variables, the apparent advantage in long-term survival of the angioplasty cohort compared with the coronary bypass cohort is actually negated, with no significant difference in survival for the two groups. Looking at subsequent angioplasty, subsequent coronary grafting, and all combined nonfatal late events, treatment group was found to be the only significant independent variable, thereby implying that the only significant predictor of these nonfatal late events was having had percutaneous transluminal coronary angioplasty.

The success rate of percutaneous angioplasty in this report was 83% for the 389 patients undergoing this procedure between 1981 and 1986. This rate is very consistent with the success rates reported in the literature from other institutions during a similar time. Deligonul and associates [26] reported a clinical success rate of 85% for their angioplasty procedures performed between 1983 and 1986. Safian and co-workers [27] had an angiographic success rate of 82% in patients undergoing angioplasty between 1982 and 1987. The National Heart, Lung, and

Blood Institute registry [28] noted an improvement in angiographic success for angioplasty from 67% in the era 1977 through 1981 to 88% in 1985 and 1986. Thus, our results are consistent with those achieved during a similar time frame at other institutions, and serve to support our belief that the late attrition after angioplasty is not as much related to the early success rate, but is more likely a function of the atherosclerotic process and the angioplasty technique itself.

Although the early results of percutaneous transluminal coronary angioplasty have been reported in large numbers from many centers, the long-term effectiveness of the procedure, which has now been performed for more than a decade, in terms of survival and especially event-free survival have been few in number. Gruentzig and colleagues [6] presented their long-term follow-up of the early angioplasty experience in Zurich. Of the first 169 patients, the procedure was successful in 133 (79%), for whom actuarial survival was 93% at 6 years. Restenosis occurred during the first 6 months after the procedure in 30% of patients. Actuarial event-free survival, which included freedom from death, myocardial infarction, and coronary bypass grafting but not subsequent angioplasty, was 79% at 6 years. Follow-up of patients with multiple-vessel disease demonstrated a higher mortality from cardiac-related causes and poorer long-term success than for patients with single-vessel disease.

Our current angioplasty study population, which includes some patients from the early years of the angioplasty experience but more than half from 1984 through 1986, demonstrates event-free survival, which includes a need for subsequent angioplasty, of 66.0% at 5 years. This is significantly different from the event-free survival of 87.1% achieved by the coronary bypass patients at 5 years.

The statistical strength and importance of the stated results must be viewed cautiously in their application to prospective assessment of what is the best initial invasive treatment strategy for patients with ischemic heart disease. Compounding the problem of trying to extrapolate these results to our current patient population is the continuing improvement in both procedures with time. Percutaneous angioplasty in our institution currently has a success rate of greater than 90% compared with the 83% reported in this study. More than 90% of nonemergency bypass procedures now involve the internal mammary artery compared with the 9% reported here. Both of these factors could have important effects on late event-free survival. Also, although we have made every possible effort to statistically account for the important differences between the two patient cohorts, the fact that this study is retrospective and not randomized is a major shortcoming.

What we can infer from this observational retrospective study is that the performance of either procedure in our institution carries with it an acceptably low risk and a good chance of early success. The long-term impact of coronary artery bypass grafting on survival and other cardiac-related events appears to be quite good. In contrast, the long-term effectiveness of percutaneous transluminal coronary angioplasty is somewhat disappointing. The survival of these patients is excellent, but the incidence of late events significantly diminishes the efficacy of angioplasty. This is true not only for all combined events, but also for the individual events—myocardial infarction, subsequent angioplasty, and subsequent coronary bypass grafting.

Of note is that the attrition after angioplasty is not due only to restenosis. Also, although the occurrence of early restenosis causes a rather important early decline in the actuarial curve, there is a definite incidence of restenosis over time.

The disparity between the long-term efficacy of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty was somewhat surprising, but on reflection, there may be several reasons why we might have predicted this result. First, coronary artery bypass grafting is uniformly directed at complete revascularization. In the long run, this is found not only to yield lower in-hospital event rates, but also to improve long-term survival and symptom relief [29–31]. Percutaneous transluminal coronary angioplasty, on the other hand, is frequently an incomplete revascularization. The incompleteness of the revascularization is due not only to the fact that frequently not all arteries with disease are dilated, but also to the fact that even those arteries that are dilated commonly do not have complete relief of the stenosis [32]. Second, as previously described, coronary artery bypass grafting is performed in such a manner that the lesion itself is generally not disrupted. Care is taken to perform anastomoses to the most normal segments of the artery wall. Angioplasty, on the other hand, depends on mechanical disruption of the artery wall. That this might lead to early events has been previously mentioned, but one must also remember that the benefit of angioplasty is dependent to a great extent on the remodeling of the artery wall after its disruption. This remodeling is basically a form of the predilection of the human body to form scar in response to localized injury. This may be why adjuvant treatment of angioplasty patients with various thrombolytic agents and varying inflation protocols at angioplasty have failed to substantially alter the incidence of restenosis. Neither coronary artery bypass grafting nor percutaneous coronary angioplasty do anything to stop the process of atherosclerosis; indeed, both procedures probably serve to accelerate the disease process in certain patients. Coronary artery bypass grafting frequently causes progression of lesion severity proximal to patent grafts because of changing flow phenomena and occasionally to the arterial tree near the areas of distal anastomosis because of localized trauma. Angioplasty creates arterial trauma in an already diseased arterial segment, thus potentially accelerating the scar formation component of the atherosclerotic process. In retrospect, it is really quite surprising how successful angioplasty is as a procedure, and this finding emphasizes once again the generally forgiving nature of the coronary arteries to localized trauma.

The fact that the angioplasty patient population evaluated in this study has a significantly poorer event-free survival than the coronary bypass patients, both in terms of combined morbidity and mortality and in terms of each nonfatal event, raises an important question about whether or not angioplasty has been successful in accomplishing the purpose for which it was designed. Coronary artery bypass grafting and percutaneous transluminal coronary angioplasty are two very different procedures that have been applied in many institutions for different reasons.

Initially, angioplasty was not viewed as a technique that would eliminate the need for a coronary bypass operation. On the contrary, the most common contention was that angioplasty would delay coronary bypass grafting in patients who were either not yet sufficiently symptomatic to warrant surgical intervention or who did not have symptomatic left main or triple-vessel coronary artery disease as an indication for operation. In fact, the majority of patients undergoing angioplasty had single-vessel disease with moderate symptoms. In the era before percutaneous transluminal coronary angioplasty, these patients would not have been considered candidates for coronary artery bypass grafting in many institutions. They were, however, thought to be good candidates for the new procedure of angioplasty in the hope that it might be possible to delay the subsequent surgical intervention. In addition, angioplasty was thought to be advantageous because it was simpler, quicker, less traumatic, and less expensive, and would require a shorter hospital stay.

We have previously observed that there are no good prospective randomized comparisons of angioplasty with coronary bypass grafting. Even more glaring, however, is the absence of the comparison of percutaneous transluminal coronary angioplasty with continued medical therapy. The somewhat disappointing event-free survival rate that we documented for our angioplasty patients calls into question the contention that angioplasty does successfully provide a large number of patients who are not yet considered candidates for bypass grafting with an event-free interval prior to the time that that procedure becomes an appropriate invasive intervention.

Finally, although this study provides some of the longest-term follow-up of a comparative nature between the two procedures, it truly cannot be described as long term. In fact, it is only midterm. The relative advantage seen for coronary artery bypass grafting in this study may begin to deteriorate in subsequent years as the coronary bypass patients begin to experience the complications associated with bypass graft attrition. If restenosis is the Achilles' heel of percutaneous angioplasty, then graft failure is the Achilles' heel of coronary artery bypass grafting. Only longer-term follow-up will determine whether the significant differences noted for the two procedures in our institution continue or are altered by time.

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DISCUSSION

DR ELLIS L. JONES (Atlanta, GA): I congratulate Dr Akins for a wonderfully presented paper, but I think that this study emphasizes the continuing need for a randomized trial to analyze the differences in outcome between surgical and angioplasty patients. In this study and all others, most patients undergoing angioplasty have single-vessel disease and most surgical patients have triple-vessel disease. I do have some concerns and reservations regarding this study, although, of course, as a surgeon I am in basic sympathy with its results and conclusions.

I think any time the results of only one surgeon are presented, a natural unintended bias is difficult to exclude. Was Dr Akins turning down bad-risk patients, thereby rendering this recent operative series, 1981 through 1986, unrepresentative of current surgical experience nationally? Were the patients who might have had multivessel angioplasty at other institutions appearing as surgical candidates on his own surgical schedule?

I find it most interesting, and I think unusual, that in only 88 of the 1,000 coronary bypass patients was the internal mammary artery used. I think it is most unusual also in a recent surgical series that the operating mortality was only 0.4%. I am not surprised that the actuarial freedom from subsequent infarction, angioplasty, or bypass procedure was high in the coronary bypass group. I think the mean follow-up of the surgical patients was only 3 years and that of the angioplasty group, only 2 years. We know that surgical patients do very well for the first 8 to 10 years of follow-up, and angioplasty patients have the majority of their serious events between 6 to 12 months after the procedure. This could be a basic criticism of the paper, but I also think it is a limitation of reporting cohorts of patients with short follow-up intervals.

I noted in my review of the manuscript that only 15% of Dr Akins's bypass patients were women compared with 23% in our 1987 series. Although this study was intended to compare differences in early results between angioplasty and coronary bypass, which here heavily favors coronary bypass, I am distracted by the uniqueness of the surgical population. Are the extremely low operative mortality of 0.4% and the essential absence of morbidity in 1,000 consecutive patients enrolled in the study up until 1986 (by one surgeon) truly reflective of the experience of cardiac surgeons nationally? Has not the effect of the proliferation of angioplasty been to reduce the number of good-risk patients in almost all institutions, with the result that surgeons operate on older, sicker patients with complex medical problems?

Our experience at Emory University Hospital has changed dramatically between 1981 and 1987. Nine percent of the entire population in the study of Dr Akins was 70 years old or older. This was a situation that existed at Emory in 1981 (9.1%). In 1987, 22% were 70 years old or older. Our results have changed dramatically since 1981. Intraaortic balloon pumping was used in 1.4% of patients in 1981 but rose to 4% last year. The mortality increased from 1.1% to 3%.

The incidence of optimal patients in our own series, ie, those less than 65 years of age and with an ejection fraction of 50% or higher, also has changed dramatically. These optimal patients represented 33% of the total 1981 surgical cohort. By 1987, this percentage had decreased to 20%. Clearly, the operative results in any series of patients undergoing bypass grafting depend on the frequency distribution of optimal patients within the series.

I apologize to Dr Akins for dwelling on one aspect of his study, but the cohort of 1,000 consecutive patients undergoing bypass was so striking it deserved special comment. If this information were quoted in the future but not understood, it might have serious secondary effects. I congratulate him, however, on a splendid consecutive series.

DR AKINS: I thank Dr Jones for his usual cogent discussion of the information presented.

Clearly this study cannot be talking about 5-year actuarial event rates and at the same time about surgery as performed today. In my own practice of cardiac surgery, currently 95% of my patients receive an internal mammary artery graft, 24% are older than 70 years, and women account for 22% of the population. Angioplasty in our institution did not grow as rapidly as it did at Emory. Consequently, in the early years of this study, we did not see the change in our patient population as rapidly as Emory saw it in theirs. However, we can talk about those data available to us that provide sufficient long-term results. One cannot talk about long-term follow-up of operations done within the last several weeks.

The surgical mortality achieved in this series is not extraordinary. Dr Rankin from Duke has published a series involving patients having elective coronary bypass; the mortality rate was 0.4%. The Cleveland Clinic, in an 11-year follow-up of patients who had coronary bypass grafting, had a cumulative mortality rate of 0.9%. Therefore, I do not think that the early results in this study are necessarily unusual. The important thing is not to focus so much on early event rates, but on the late event rates for the two procedures.

Given the inherent limitations of the study design, the statistical strength and importance of the results must be used cautiously in any prospective assessment of which procedure is the better initial invasive treatment for patients with ischemic heart disease. Also, although this study provides some of the longest follow-up of a comparative nature between coronary grafting and angioplasty, it cannot truly be described as long term; it is only midterm. The relative advantage seen for coronary grafting may, over subsequent years, begin to deteriorate as coronary bypass patients begin to experience the complications associated with bypass graft attrition.

However, the results of this study raise the important question of whether angioplasty has been successful in accomplishing the purpose for which it was originally intended, namely, to delay coronary bypass operation in patients who either were not sufficiently symptomatic or did not have extensive left main or multiple-vessel coronary disease as an indication for a bypass graft procedure. The significantly poorer event-free survival documented in this study for our angioplasty population, even though they were at significantly lower risk, suggests that percutaneous transluminal coronary angioplasty has not been successful in providing an event-free interval and may have contributed to the premature entry of many patients with coronary disease into the invasive treatment aspect of cardiac care.

Notice From The Society of Thoracic Surgeons

The Society of Thoracic Surgeons is pleased to announce two new membership categories, International and Candidate, with the following qualifications.

International Members: Members of this category shall reside outside the United States and Canada. Their training in this specialty shall be considered equivalent to that of active members. They shall have achieved appropriate certification or recognition of their achievements in this specialty in their country and must devote the majority of their professional efforts in the interests of the specialty. Appropriate documentation of professional achievements shall be provided to the Membership Committee. Members residing in countries other than the United States and Canada elected to membership before October 1, 1988, shall maintain their current status until eligible for Senior Membership or Inactive Status. The dues will be similar to those charged for Active Members.

Candidate Members: Members of the Candidate Group shall be enrolled in a thoracic and cardiovascular training program accredited by the Residency Review Committee for Thoracic Surgery under the authority of the Accreditation Council for Graduate Medical Education or in a similar program approved for training by the Royal College of Surgeons of Canada. Also, individuals who have completed their training in one of the above programs and are in the process of acquiring certification by the American Board of Thoracic Surgery or the Royal College of Surgeons of Canada are eligible for this type of membership. Upon obtaining and presenting appropriate qualifications for active membership, a member of the Candidate Group, upon request and recommendation of the Membership Committee, Council, and membership, shall be advanced to this category in The Society and shall become subject to all of the responsibilities, rights, duties, assessments, and privileges of an Active Member. Membership in the Candidate Group will be for a maximum of 5 years following completion of training. The annual dues are $55.

Dues for both groups include a subscription to *The Annals of Thoracic Surgery*. The 1989 application deadline is May 1st. Applications for both types of membership are available from The Society of Thoracic Surgeons, 111 East Wacker Drive, Suite 600, Chicago, IL 60601; telephone (312) 644-6610.

Late Reoperation for Systemic Atrioventricular Valve Regurgitation After Repair of Congenital Heart Defects

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Since 1979, 17 infants and children have undergone reoperation for systemic atrioventricular (AV) valve regurgitation 6 weeks to 7 years after repair of congenital heart defects. Prior operations were repair of incomplete or complete AV canal (14 patients), Mustard repair of complex transposition of the great arteries including ventricular septal defect closure (2 patients), or first-stage operation for hypoplastic left heart (1 patient). Age ranged from 6 months to 11 years. In 12 of the 17 patients (10, AV canal; 1, transposition; 1, hypoplastic left heart), valve reconstruction was possible. Operative techniques included a combination of septal cleft approximation, leaflet resection, commissural annuloplasty, or ring annuloplasty. There were no operative deaths, and there were no reoperations in the repair group. The condition of these patients has improved. Follow-up ranges from 1 month to 9 years (mean follow-up, 4.1 years). Five of the 17 patients (4, AV canal; 1, transposition) underwent valve replacement. There were no operative deaths. Follow-up ranges from 3 to 8 years. Three patients later underwent re-replacement of the prosthetic valve; there was 1 late death. The condition of all 4 survivors is improved. Substantial AV valve regurgitation can occur months or years after repair of congenital heart defects. A combination of reconstructive techniques may be useful in preserving native valve function and avoiding systemic AV valve replacement.

(Ann Thorac Surg 1989;47:517–23)

Systemic atrioventricular (AV) valve regurgitation can occur months or years after repair of congenital heart defects. In an AV canal defect, the left-sided AV valve (the systemic AV valve) is a trileaflet structure [1]. Primary repair of this congenital heart defect often involves an attempt to reduce systemic AV valve regurgitation [2, 3]. Surgical repair of transposition of the great arteries with ventricular septal defect (VSD) utilizing the Mustard or Senning approach requires operation through the tricuspid valve orifice. Late follow-up of these patients often reveals the development of systemic AV valve insufficiency [4]. In addition, AV valve regurgitation can develop in some patients with hypoplastic left heart syndrome [5].

When systemic AV valve regurgitation appears after a previous surgical repair, a therapeutic dilemma exists. Bioprosthetic valves are known to fail rapidly in infants and children when utilized as the systemic AV valve [6]. Mechanical valve replacement requires long-term anticoagulation [7]. Any prosthetic AV valve replacement limits growth of the annulus. Reconstruction of a systemic AV valve that has previously been operated on is an attractive solution to these difficult clinical problems.

Since 1979, we have performed reoperations on 17 patients with substantial systemic AV valve regurgitation. In all patients, the valve was trileaflet. No patient in this series had an anatomical mitral valve as the systemic AV valve. In 12 of the 17 patients, a reparative procedure was possible. This report details the indications, techniques, and results of attempts to preserve native systemic AV valve function in infants and children.

Material and Methods

Patient Population

Between November 1979 and August 1988, 17 children aged 7 months to 19 years (average age, 6.2 years) underwent reoperation for major systemic AV valve regurgitation. The interval between the primary operation and reoperation ranged from 3 weeks to 7 years (mean interval, 2.8 years). The indications for reoperation were the following: New York Heart Association class IV congestive heart failure (4 patients), hemolysis and class III congestive heart failure (2 patients), severe AV valve regurgitation with increasing cardiomegaly and decreased ventricular function (7 patients), residual partial anomalous pulmonary venous drainage and severe AV valve regurgitation with increasing cardiomegaly (1 patient), residual atrial septal defect, severe AV valve regurgitation, and increasing cardiomegaly (1 patient), increasing cardiomegaly and AV valve regurgitation after subacute bacterial endocarditis (1 patient), and the development of

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discrete subaortic stenosis with increasing cardiomegaly and increasing AV valve regurgitation (1 patient).

Eleven of the 17 patients had undergone previous repair at Children's Hospital and Health Center of San Diego. Six patients had been previously operated on elsewhere. The diagnoses included complete AV canal (large unrestrictive VSD) in 7 patients, 1 of whom also had severe tetralogy of Fallot and 1, an additional large apical VSD and cor triatriatum dexter. Six patients had an incomplete AV canal (4 had no VSD and 2 had the intermediate form of AV canal with a small VSD closed by direct suture technique), 2 of whom had a double-orifice "mitral" valve [8]. There was 1 patient with an AV canal type of left-sided AV valve (trileaflet) that had previously been reconstructed. This patient had no atrial septal defect or VSD. Two patients had previously undergone a Mustard procedure with transatrial closure of a large VSD, and 1 patient had previously had a first-stage operation, which included tricuspid annuloplasty, for a hypoplastic left heart syndrome variant.

The prior operative report was available on all 14 patients undergoing reoperation after previous repair of an AV canal type of defect. In 13 patients, sutures had been placed in the septal cleft at the time of previous repair. In 1 patient with incomplete AV canal, the atrial septal defect was closed and no sutures were placed in the septal cleft at the time of primary repair because of preoperative and intraoperative assessment of AV valve function. There were 7 patients who had undergone previous repair of a complete AV canal. Repair was accomplished with a single patch in 4 of these patients and with two patches in 3. In 6 of the 7 patients with complete AV canal, the common leaflets were tethered to the septum. Only 1 patient had a type C complete AV canal with free-floating anterior and posterior leaflets at the time of primary repair.

Surgical Technique

Reoperation was carried out utilizing continuous cardiopulmonary bypass with moderate hypothermia in all patients but 1. One operation was performed using the technique of deep hypothermia and circulatory arrest. Intermittent crystalloid or blood cardioplegia was utilized for myocardial preservation. Myocardial temperature was measured, and myocardial cooling was enhanced by the use of topical slush or iced saline solution. Exposure of the left-sided AV valve was obtained with an incision posterior to the interatrial groove except in the youngest patient and in patients requiring repair of right atrial abnormalities for residual defects. In those patients, exposure of the left-sided AV valve was obtained through the atrial septum.

The abnormal AV valve was inspected after cardioplegic arrest. In all patients, the ventricle was distended with saline solution injected through a rubber catheter. In 1 patient, retrograde filling of the ventricle through an apical vent catheter was utilized to evaluate AV valve function. Leaflet apposition, leaflet prolapse, and the anatomical configuration of the valve were noted. It was apparent in all patients that some or all leakage was associated with the septal cleft. Two patients had a double-orifice "mitral" valve with restricted leaflet motion. One patient had partial dehiscence of the anterior portion of the left-sided AV valve common leaflet. This patient had previously been treated for bacterial endocarditis. It was not possible to determine if the dehiscence had been present since the repair or if it had developed during or been worsened by the endocarditis episode.

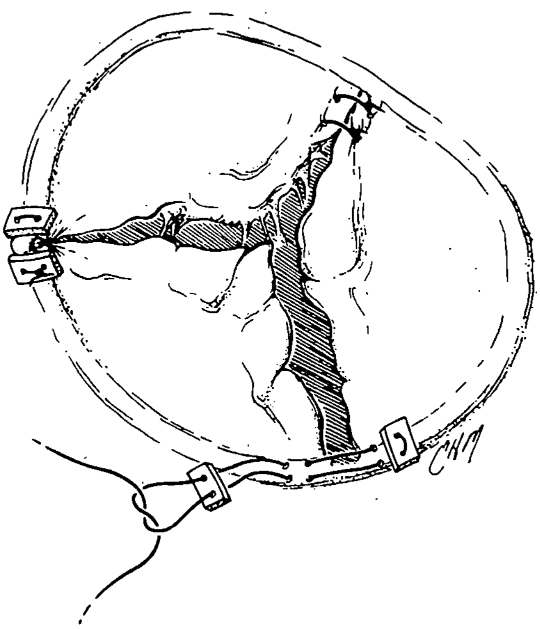

Fig 1. Techniques for repair of left-sided atrioventricular (AV) valve in AV canal defect. Teflon pledget–reinforced annuloplasty sutures are utilized to narrow the commissures. Additional sutures are placed in the septal cleft to reduce regurgitation.

Techniques in the AV valve repair group included the placement of additional sutures in the septal cleft in all patients (Fig 1). In 1 patient, a second cleft in the posterior leaflet was also closed. Annuloplasty sutures were utilized in 7 of 10 patients [9]. In 3 patients, annuloplasty sutures were placed in both of the nonseptal commissures (posterior and anterior commissures). A single annuloplasty suture was utilized in 4 patients. Two patients underwent annuloplasty of the posterior commissure and 2 underwent annuloplasty of the anterior commissure. One of these patients also underwent placement of a Duran ring. Partial dehiscence of the leaflet was repaired with a pericardial patch in 1 patient. Another patient underwent chordal shortening, leaflet resection, and implantation of a Duran ring [10].

Patients undergoing repair of a regurgitant anatomical tricuspid valve included 1 patient with a hypoplastic left heart syndrome variant. In this patient, a previous annuloplasty suture had been placed at the junction of the septal and posterior leaflets. At reoperation, an additional annuloplasty suture was put at the junction of the septal and anterior leaflets with improvement in the degree of regurgitation. One patient with transposition of the great arteries had deficient chordae in the region of the septal leaflet over the VSD patch. The leaflet was prolapsing. A triangular segment of the septal leaflet was resected, and the leaflet was repaired. A 30-mm Carpentier tricuspid ring [11] was implanted.

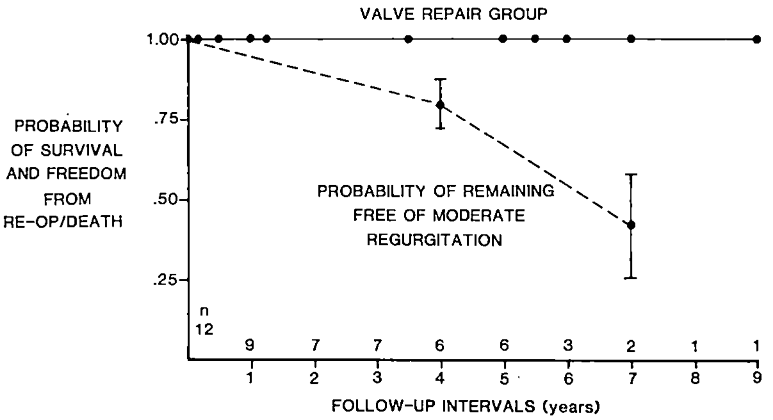

Fig 2. Actuarial probability of survival and freedom from reoperation for all patients undergoing valve repair. The graph includes operative mortality. All patients are alive, and no patient has required reoperation. The broken line depicts the actuarial probability of remaining free from moderate regurgitation. Moderate regurgitation is defined as atrioventricular valve regurgitation associated with an increased cardiothoracic ratio or evidence of systemic ventricular dysfunction. Bars indicate ± one standard error.

Patients undergoing valve replacement had anatomical problems not amenable to repair. In 1 patient with severe hemolysis after extensive reconstruction of an AV canal type of left-sided AV valve, we were uncertain that further surgical intervention would relieve the hemolytic process; therefore, the valve was replaced. Another patient with a double-orifice "mitral" valve and incomplete AV canal had inadequate chordal support of the posterior leaflet. This patient also had hemolysis. After repair of tetralogy of Fallot and complete AV canal, another patient (the oldest in the series) had inadequate leaflet tissue to effect a satisfactory repair of the left AV valve. In addition, pulmonary valve implantation was necessary. Two patients (1 with transposition of the great arteries plus VSD and 1 with complete AV canal) had dense adherence of a portion of the AV valve leaflet to the VSD Dacron patch. Two of these 5 patients underwent replacement with a porcine bioprosthesis, 2 with a Björk-Shiley valve, and 1 patient with a St. Jude bileaflet valve.

Intraoperative assessment of the quality of repair was carried out in all patients. After visual inspection of leaflet coaptation and function based on injection of saline solution, the repair was completed. After the discontinuation of cardiopulmonary bypass, left atrial pressure was measured in all patients. In the first 12 patients, repair was also assessed by the use of a sterile stethoscope. The last 5 patients in the series underwent reparative operations, and each patient was assessed by intraoperative color flow epicardial two-dimensional echocardiography before and after operation. At the completion of operation, left atrial pressure ranged from 8 to 17 mm Hg. No patient had a clinically significant V wave in the left atrial pressure tracing. All patients had a reduction in or elimination of the systolic murmur. Patients undergoing intraoperative echocardiography had satisfactory to excellent valve function with trivial or minimal AV valve regurgitation. In some views, the valve was completely competent.

Results

All 17 patients survived operation, and the condition of each was subjectively and objectively improved by valve repair or replacement.

Repair Group

No patient in the repair group has required reoperation (Fig 2). Ten of the 12 patients are free from any major or worrisome residual AV valve regurgitation. In each of these 10 patients, the cardiothoracic ratio has returned to normal and the patients are on a regimen of minimal or no medication. No patient has any signs or symptoms of cardiac decompensation. Three patients have no detectable murmur, and 7 have a minimal regurgitant murmur. Serial follow-up echocardiography reveals trivial to mild residual regurgitation in these 10 patients.

The 2 other patients undergoing repair had very satisfactory early results. In 1 of them (transposition of the great arteries and VSD), moderate anatomical tricuspid valve regurgitation developed 7 years after reoperation for repair of the tricuspid valve. This patient had undergone leaflet resection and repair with implantation of a Carpentier tricuspid valve ring. For 7 years she was completely asymptomatic and took only Lanoxin (digoxin). The maximal exercise test was at the lower limits of normal working capacity with a normal blood pressure response. Seven years after valve repair, she was noted to have increasing cardiomegaly on the standard chest roentgenogram. This correlated with increasing tricuspid regurgitation detected by two-dimensional echocardiography with color flow mapping. The patient has responded to unloading therapy, and she continues to have a stable maximal exercise test. Close follow-up is underway. If further objective signs of deterioration occur, valve replacement will probably be necessary.

The other patient had originally undergone incomplete AV canal repair in 1978 at another institution. In 1983, he was seen with severe left-sided AV valve regurgitation and gross cardiomegaly. He had bradycardia caused by intermittent second-degree heart block. Cardiac catheterization revealed a residual atrial septal defect with a 2:1 left-to-right shunt. At reoperation, a double-orifice left-sided AV valve was detected. Repair consisted of additional suturing of the septal cleft and two separate annuloplasty sutures. The double orifice was created by a bridge of leaflet tissue connecting the posterior common leaflet with the leading edge of the lateral leaflet. No surgical procedure was performed on the area of leaflet

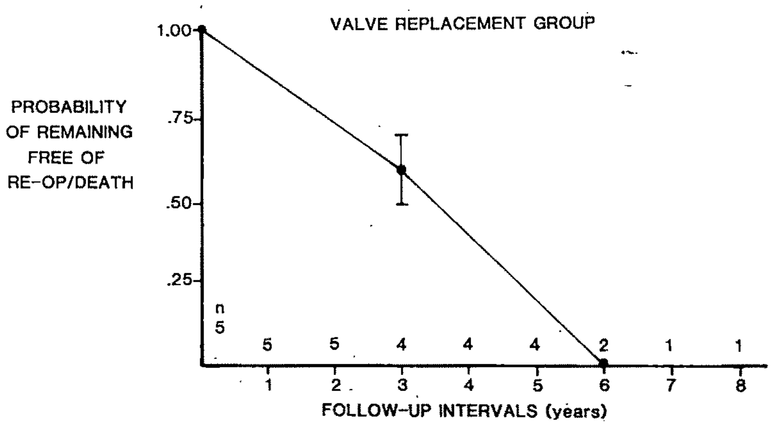

Fig 3. Actuarial probability of remaining free from reoperation or death for all patients undergoing valve replacement. Operative mortality is included; there were no operative deaths. One patient died 3 years after re-replacement of a mechanical valve. Bars indicate ± one standard error.

fusion. The patient had an excellent objective response to operation, and a pacemaker was not necessary for 4 years.

In early 1988, the patient was seen with increasing cardiomegaly and clinical evidence of increasing AV valve regurgitation. In addition, substantial resting bradycardia associated with second-degree heart block had developed. Holter monitoring revealed prolonged episodes of heart rate less than 55 beats per minute. The patient underwent implantation of a dual-chambered AV sequential pacemaker (DDD) with reduction in size of the cardiac silhouette. Follow-up echocardiography indicated reduced regurgitation with AV sequential pacing. The patient remains asymptomatic with normal exercise tolerance. The cardiothoracic ratio is now within the normal limits.

In 1 patient, major hemolysis developed after late reconstruction of the left-sided AV valve. This patient was born on October 18, 1973. At 2 months of age, she underwent pulmonary artery banding at another institution. In 1978, she underwent repair of complete AV canal and debanding at another institution. In February 1985, she underwent extensive reconstruction of the left-sided AV valve for severe regurgitation associated with decreased exercise tolerance and progressive cardiomegaly. The cleft had been completely closed at the first repair.

At operation, the region of the septal cleft was prolapsing and poorly supported. The prolapsed segment of the conjoined leaflets was resected, and a septal annuloplasty suture was placed. The cleft was then closed with interrupted sutures. Chordae tendineae of the anterior and posterior common leaflets were shortened, and a 29-mm Duran ring was implanted. The patient had a very satisfactory hemodynamic response to operation.

However, six weeks after operation, she was noted to have critical hemolysis. Hematocrit fell to 22%. Medical therapy including iron replacement was instituted. No transfusions were ever necessary. In March 1986, 1 year after secondary reconstruction of the AV valve, repeat catheterization was performed. Left ventricular function was normal, and mild residual regurgitation was identified. The end-diastolic gradient was 2 mm Hg. The hemolysis continued to improve without the need for transfusion. In 1988, the hematocrit was 38% and the reticulocyte count, 3%.

In summary, the repair group has enjoyed a very satisfactory short- to medium-term palliation. Follow-up ranges from 1 month to 9 years (mean duration, 3.7 years). The duration of follow-up is not long enough to predict the long-term results. However, it is clear that secondary reconstruction of the systemic AV valve can prevent or delay the need for valve replacement in infants and young children.

Valve Replacement Group

All patients survived operation (Fig 3). Three patients underwent re-replacement of the prosthetic valve at 3 years, 3 years, and 6 years. The rate of valve failure was probably accelerated by the use of bioprosthetic valves early in the series.

One patient died 6 weeks after re-replacement of a mitral prosthesis. She had originally undergone repair of complete AV canal with cor triatriatum dexter and an additional large apical VSD. She underwent replacement of the left-sided AV valve 6 weeks after repair of the AV canal. Repair was necessitated by the fusion of the posterior AV valve leaflet to the Dacron patch. The patient had a very small annulus, and a 17-mm Björk-Shiley valve was implanted.

Three years later, the patient enjoyed excellent palliation. However, she returned with symptoms of mitral stenosis. She had clearly outgrown the very small mechanical valve. At the next operation, a 21-mm St. Jude valve was implanted in the supraannular position. The postoperative course was smooth, and she was discharged on a regimen of reduced medications. Six weeks after replacement of the mechanical valve, she died suddenly at home. At autopsy, no cause of death was detected.

In summary, the valve replacement group has enjoyed excellent palliation. Follow-up ranges from 3 to 8 years (mean duration, 5.2 years). The 4 survivors are free from cardiac symptoms. All now have mechanical valves, and they are on a regimen of Coumadin (crystalline warfarin sodium).

Comment

Systemic AV valve regurgitation can occur in a variety of congenital heart conditions. Other authors [12, 13] have detailed the use of reconstructive techniques in the treatment of congenital mitral insufficiency and for patients who had rheumatic heart disease. This report concentrates on the use of reparative techniques for the treatment of patients with late AV valve regurgitation after complete repair of a congenital heart defect. None of the patients in this series had an anatomical mitral valve as the systemic AV valve.

There has been some debate regarding the appropriate surgical technique for primary repair of complete and incomplete AV canal [2, 3, 14–16]. Advocates of the one-patch or two-patch technique cite comparable short-term and long-term results.

The treatment of the septal cleft or commissure is also an area of concern [3]. In this series, all patients undergoing reoperation after prior repair of AV canal had evidence of regurgitation through the septal cleft. In all patients, we placed additional sutures in the septal cleft; in 1 patient, the septal cleft was excised and reconstituted to eliminate leaflet prolapse and narrow the annulus. It is difficult to determine whether regurgitation through the septal cleft is the result of inadequate surgical intervention at the time of primary repair or the result of growth and development of the AV valve in later years.

One patient in this series underwent patch closure of a primum atrial septal defect with no attempt at repair of the left AV valve. Based on preoperative catheterization and echocardiography, there was no evidence of AV valve incompetence at the time of primary repair. Six years after primary repair, the patient was seen with congestive heart failure. At operation, it was found that the cleft had widened and the edges of the anterior and posterior leaflets were fibrotic and thickened. Complete competence of the valve was restored by placing sutures in the cleft, performing an annuloplasty suture at the posterior commissure, and implanting a Duran ring. The case of this patient suggests that a trileaflet AV valve that is competent in early infancy can develop regurgitation years later [16]. Whether or not primary repair should include sutures in the septal cleft of a patient with a competent left AV valve is debatable.

Indications for operation in this series were heart failure, decreased exercise tolerance, or objective evidence of cardiac deterioration in the absence of symptoms. In infants and small children, cardiac symptoms may not be obvious until overt congestive failure occurs. All patients undergoing repair at our institution are followed closely with serial chest roentgenograms and echocardiograms. When a patient with a murmur of systemic AV valve regurgitation shows evidence of cardiomegaly (cardiothoracic ratio >0.55), two-dimensional echocardiography and cardiac catheterization are indicated. These studies can define left ventricular function and assess valvular anatomy. In addition, new lesions may have developed that can contribute to AV valve regurgitation, eg, subaortic stenosis or leaflet dehiscence after endocarditis. Because repair is likely in most patients with AV canal, operation should be considered before overt congestive heart failure occurs and certainly before pulmonary hypertension is detectable.

The surgeon can predict the repairability of the valve on the basis of the previous operative report, catheterization and echocardiographic data, and clinical presentation. Our data indicate that a patient seen with major hemolysis after a previous attempt at repair will probably require valve replacement. The presence of class IV congestive heart failure does not mean that valve replacement is necessary. Two of 4 patients seen with class IV congestive heart failure underwent successful repair with excellent long-term results. In our experience, an anatomical tricuspid valve can be repaired. If an aggressive attempt has been made to repair a markedly abnormal valve at the time of primary operation, it is unlikely that a secondary reparative procedure will be successful.

The techniques utilized for a repair of the left AV valve in patients with AV canal are a combination of standard operative techniques [3, 9–11]. In all 10 patients undergoing late repair after correction of an AV canal defect, the septal cleft was repaired. Single or double annuloplasty sutures can be placed, and in some patients a ring annuloplasty can be useful. We have utilized the Duran ring for the left AV valve and a Carpentier ring in 1 patient with transposition. Leaflet resection and chordal shortening procedures can also be useful in select instances.

One patient had substantial hemolysis after secondary repair. This patient never required a blood transfusion, and long-term follow-up revealed progressive improvement. Three and one-half years after repair, the hemolysis is not clinically detectable, and the patient has a normal hematocrit with a slightly elevated reticulocyte count. In general, conservative treatment of postoperative hemolysis should be attempted. In our experience, serious hemolysis associated with the need for transfusion almost always requires valve replacement.

In summary, the development of systemic AV valve regurgitation after prior repair of a congenital heart defect does not mean that AV valve replacement will be necessary. Our experience indicates that commonly utilized reparative techniques can be offered to infants and children with major AV valve regurgitation. Analysis of the previous operative report and the clinical presentation of the patient in conjunction with two-dimensional echocardiography and angiography can predict the likelihood of a late reconstruction. The short- to medium-term follow-up of our patients indicates excellent subjective and objective improvement. Repair avoids valve replacement with the requirement for anticoagulation in infants and small children. The techniques used should allow for growth and development of the annulus. Most of these patients will probably require valve replacement in later life. We try to avoid the use of a ring technique unless an adult-sized ring can be implanted.

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DISCUSSION

DR WILLIS HOWARD WILLIAMS (Atlanta, GA): Dr Lamberti and his colleagues deserve our congratulations for having achieved these excellent results. They report no operative deaths, no need, to date, for reoperation, and both subjective and objective improvement in 12 of 17 infants and children in whom they were able to salvage the native mitral valve in a secondary operation to correct mitral regurgitation. I applaud their efforts to avoid the implantation of a prosthetic mitral valve, both to preserve growth potential and to avoid the need for anticoagulation.

As 13 of these 17 children had either complete or incomplete forms of AV canal or AV septal defects, I shall confine my comments to these diagnoses. I note that in 13 of the 14 children having AV septal defects, sutures were placed in the cleft between the anterior and posterior components of the mitral apparatus at the first operation. My first question is simply an inquiry as to why the authors were successful at a second operation when they had in many cases apparently failed earlier. Did the sutures in the cleft actually promote the development of regurgitation because of the deformity caused in the leaflets and the potential restriction of the growth of the leaflets? Did the authors adhere in their initial operation to the admonitions of Dr Starr to shorten the top of the VSD patch in the two-patch operation or to create a narrow waist at the level of valve leaflet attachment when a single patch is used? Was an attempt made at the first operation to assure a broad surface of anterior and posterior leaflet coaptation by attaching the leaflet edges well down within the cleft in the VSD patch as advocated by Professor Carpentier? Does this group of patients represent persistent or recurrent or new mitral regurgitation or a combination of these? How often should we expect the need for reoperation? From what total number of patients having AV canal repair was this group of 14 having secondary repairs for mitral regurgitation derived?

Finally, in a recent review of 97 primary and secondary repairs of complete AV canal based on our experience at Emory, we noted that the infants without Down's syndrome required initial surgical intervention earlier in life than did those with Down's syndrome. Fifty percent of the infants without this syndrome required operation by the age of 2.5 months, whereas only 10% of infants with Down's syndrome had required operation at that relatively young age. We believe that both a more rapid fall in pulmonary vascular resistance and a greater degree of mitral regurgitation or AV valve regurgitation contribute to this earlier need for operation.

We also found the mitral valve much more difficult to reconstruct and valvular competence more elusive in the infants without Down's syndrome, particularly those who had been treated by a previous pulmonary artery band, a shunt, or both. The late survival was much lower—65%—at 5 years in the group without Down's syndrome having secondary repair than in the primary repair groups and in the children with Down's syndrome. In these groups, survival approached 90% at 5 years.

Have you noted any differences in your ability to construct a competent mitral apparatus in infants with Down's syndrome versus infants without it or in those having previous palliation by a pulmonary artery band or shunt?

DR ROBERT W. M. FRATER (Bronx, NY): I, too, compliment Dr Lamberti on his results in a difficult group of patients, and will ask him to be more specific, if it is possible, about the mechanisms of insufficiency.

In the patients with AV canal with recurrent insufficiency whom I have seen, it is common to find that the anterior cusp fails to meet the posterior cusp. The mechanism sometimes has been that in the previous operation, an excessive amount of the anterior cusp has been taken up in the course of attaching it to a single patch. Alternatively, an excessive amount of cusp tissue is taken up in suturing the cleft, changing the free edge of the conjoined new cusp from a bow to a straight line. Dr Lamberti has apparently seen failure of anterior and posterior apposition, and has used annuloplasty as the treatment.

I propose an alternative that I have found very useful. Not wanting to do an annuloplasty on a child, I have instead extended the anterior cusp, detaching it from the patch used to close the VSD and atrial septal defect and extending it with a gusset of xenograft pericardium. I have done the same thing primarily in cases in which it has been apparent to me during the initial repair that the anterior cusp was going to be small. Dr Lamberti, would you comment on this technique?

DR LAMBERTI: I thank the discussants. Time did not permit me to cover many of these important points, some of which are discussed in the manuscript.

Does the need for a secondary repair operation indicate an inadequate primary repair? I think that the patient with a completely competent AV valve at the time of the first operation illustrates an interesting point. Six years later, the valve had become incompetent. The natural history of the left-sided AV valve in AV canal can reveal progressive deterioration of function in a small percentage of patients. We now believe that the surgeon should be more aggressive at the time of primary repair. In recent years, we have placed annuloplasty sutures when appropriate to minimize the degree of regurgitation at primary repair.

We do adhere in general to the admonitions of Drs Starr and Carpentier. However, no attempt was made to turn the leaflets into the VSD patch in any of our patients, as recommended by Carpentier. We do believe that the VSD patch should not be oversized because a large patch can separate the coaptation line of the leaflets. Not all of the patients underwent the first repair at our hospital, and therefore the 14 patients with AV canal do not represent the residuum of our series.

As for incomplete or intermediate forms of AV canal, we have operated on 32 patients with no deaths. Four of the patients came back for reoperation, and we thought they had predisposing lesions. In 1, subaortic stenosis, which would aggravate regurgitation, developed. One patient had had no sutures placed and had a totally competent left AV valve at primary repair. One infant had severe preoperative mitral regurgitation. In retrospect, we believe that we were not aggressive enough at the time of primary repair in that infant. The valve was reoperated on 3 weeks after primary repair, and the result is excellent at 7 years. I think the moral here is that one should be as aggressive as possible in dealing with the systemic AV valve.

In the group of patients with complete AV canal the operative mortality was 12%. Four required reoperation, 1 of whom had sustained bacterial endocarditis.

We have not looked at the difference between infants with Down's syndrome and those without it. Therefore, I cannot comment on the degree of difficulty of valve repair in patients without Down's syndrome.

The question of whether AV valve regurgitation is persistent regurgitation or recurrent regurgitation can generally be determined on an individual basis. When a new anatomical lesion appears that predisposes to regurgitation, the late result is not clearly the fault of the primary surgeon, whoever he or she was.

In regard to Dr Frater's comment, I think that a part of the eclectic approach to valve repair should be leaflet advancement. This is a technique that both he and Dr Carpentier have advocated, and it may be particularly useful for an anatomical tricuspid valve in transposition of the great arteries. We did not encounter a patient for whom we thought leaflet advancement an appropriate technique. However, we did utilize a pericardial patch on the one dehiscence that we treated.

Mitral Valve Annuloplasty: The Effect of the Type on Left Ventricular Function

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This study was undertaken to determine whether rigid-ring annuloplasty and flexible-ring annuloplasty have the same effect on left ventricular function in patients with chronic mitral regurgitation secondary to degenerative disease of the mitral valve. Twenty-five patients who underwent isolated mitral valve repair and required annuloplasty were randomized into two groups: rigid-ring and flexible-ring annuloplasty. Left ventricular function was assessed by echocardiography and radionuclide angiography on the day before operation and 2 to 3 months later. Preoperative left ventricular function was similar in the two groups of patients. Postoperatively, left ventricular end-diastolic diameter and volume decreased significantly in both groups. The left ventricular end-systolic diameter and volume decreased significantly only in patients with a flexible annuloplasty ring. Left ventricular systolic function as assessed by pressure–volume relationships was significantly better in patients with a flexible ring ($p < 0.02$ by analysis of covariance), and left ventricular performance measured by stroke volume–end-diastolic volume relationships was also better in these patients ($p < 0.05$ by analysis of covariance). These data indicate that patients with a flexible annuloplasty ring have better left ventricular systolic function than patients with a rigid annuloplasty ring 2 to 3 months after mitral valve reconstruction for chronic mitral regurgitation secondary to degenerative disease of the mitral valve.

(Ann Thorac Surg 1989;47:524–8)

There is mounting evidence in the surgical literature that the mitral valve is an integral part of the left ventricle and that its anatomical presence plays an essential role in left ventricular geometry and mechanics [1–5]. The mitral annulus has a sphincterlike function, which reduces its area by approximately 26% during systole [6]. The mitral annulus is quite circular during diastole but becomes more elliptical in systole [6]. This change in size and shape is thought to be secondary to the relaxation and contraction of the basoconstrictor muscles (bulbospiral and sinospiral muscle bundles) [7]. Experimental fixation of the mitral annulus with a rigid prosthesis such as an artificial mitral valve or a rigid annuloplasty ring impairs left ventricular systolic function [2]. This study was undertaken to observe the effect of rigid and flexible annuloplasty rings on left ventricular function in patients who had mitral valve repair for chronic mitral regurgitation.

Material and Methods

Twenty-seven patients who underwent mitral valve repair because of chronic mitral regurgitation secondary to myxomatous disease were randomized into two groups: one treated with rigid annuloplasty (Carpentier's ring) and the other, with flexible annuloplasty (Duran's ring). The randomization was done in the operating room after the mitral valve was repaired and mitral annuloplasty was deemed necessary because of gross dilation of the annulus. Two patients were excluded from the study; 1 patient had substitution of a rigid ring by a flexible ring because of left ventricular outflow tract obstruction, and the other had postoperative evidence of mild mitral regurgitation by Doppler echocardiography. The remaining 25 patients underwent either rigid-ring (11 patients) or flexible-ring annuloplasty (14 patients).

All patients had chronic mitral regurgitation secondary to degenerative disease of the mitral valve. There were 18 men and 7 women whose mean age was 59 years (range, 41 to 76 years). Only 1 patient in each group was in atrial fibrillation before operation. The clinical presentation and functional class were similar in both groups. One patient from the rigid ring group and 2 patients from the flexible ring group were in New York Heart Association Functional class II, 8 and 9 patients, respectively, were in class III, and 2 and 3 patients, respectively, were in class IV.

All patients were studied by Doppler echocardiography and radionuclide angiography on the day before operation and 2 to 3 months later. Postoperative radionuclide angiograms were obtained at rest and during exercise. The radionuclide angiograms were performed with simultaneous recording of phonocardiogram, carotid artery pulse, and cuff blood pressure [8]. These measurements were made to allow us to determine systolic pressure–volume relationships and stroke volume–end-diastolic volume relationships [9]. All patients were on a regimen of Coumadin (crystalline warfarin sodium) during the first 3 postoperative months.

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Table 1. Operative Data[a]

Variable	Rigid Ring	Flexible Ring
Valve pathology		
Flail posterior leaflet	8	10
Flail anterior leaflet	2	1
Flail anterior and posterior leaflets	1	3
Valve repair		
Resection of part of posterior leaflet	8	10
Resection of posterior leaflet + shortening of chordae tendineae of anterior leaflet	1	3
Replacement of chordae tendineae with Gore-Tex sutures	2	1
Ring size (mm)	31.6 ± 1.9	32 ± 1.6
Aortic cross-clamping (min)	44 ± 9	40 ± 11
Cardiopulmonary bypass (min)	59 ± 14	54 ± 8

[a] Where applicable, data are shown as the mean ± the standard deviation.

The preoperative and postoperative changes in ventricular dimensions, volumes, blood pressure, and heart rate were analyzed by Student's *t* tests. The two groups of patients were compared by independent *t* tests and by analysis of variance when indicated. Postoperative left ventricular systolic function (pressure–volume relationships) and left ventricular performance (stroke volume–end-diastolic volume relationships) of the two groups were compared by analysis of covariance.

Results

There were no operative deaths among the 25 patients. Table 1 summarizes the operative data. Two patients in the flexible-ring group experienced serious postoperative complications. One elderly woman with chronic obstructive lung disease required 2 weeks of ventilatory support, and 1 man required reoperation in the third postoperative week because of paravalvular mitral regurgitation secondary to dehiscence of the posterior part of the mitral annulus, which had been plicated after resection of a portion of the posterior leaflet. There were no perioperative myocardial infarctions and no cases of low cardiac output syndrome.

At the end of the second postoperative month, all but 3 patients were functionally in New York Heart Association class I. Two patients from the flexible-ring group and 1 from the rigid-ring group were functionally in class II.

No patient had postoperative clinical or echocardiographic evidence of mitral regurgitation. In addition, no patient had echocardiographic evidence of left ventricular outflow tract obstruction. Table 2 shows the preoperative and postoperative echocardiographic data. Preoperative systolic and diastolic left ventricular dimensions were similar in both groups. Postoperatively, the decrease in left ventricular end-diastolic diameter was significant in both groups. The decrease in end-systolic diameter, however, was significant only in patients with flexible-ring annuloplasty ($p < 0.03$). The postoperative mitral valve orifice measured 3.41 ± 1.51 cm² in patients with a rigid ring and 2.93 ± 0.57 cm² in patients with a flexible ring (p = not significant).

Table 3 shows the radionuclide angiographic data. The preoperative left ventricular volume, ejection fraction, systolic blood pressure, and heart rate were similar in both groups of patients. Postoperatively, the end-diastolic volume index decreased significantly in both groups ($p < 0.001$), but the end-systolic volume index decreased significantly only in patients with a flexible ring ($p < 0.02$).

Postoperatively, the rise in heart rate and systolic blood pressure during maximum exercise was significant in both groups ($p < 0.001$). The rise in blood pressure in patients with a flexible ring was greater than in patients with a rigid ring. The end-systolic volume index during exercise increased slightly in patients with a rigid ring, but the difference did not reach significance. The left ventricular ejection fraction increased in both groups during exercise.

Left ventricular systolic function as measured by pressure–volume relationships (Fig 1) was distinctly better in patients with a flexible ring ($p < 0.02$ by analysis of covariance). Left ventricular performance was also superior in patients with a flexible ring ($p < 0.05$) (Fig 2).

Comment

The interactions between the mitral valve and the left ventricle are complex and not yet entirely understood. Experimental studies have conclusively demonstrated that the mitral valve plays an important role in left ventricular geometry and function [1–5]. The continuity between the mitral annulus and the ventricular wall through the chordae tendineae and papillary muscles is probably the most important factor in the valvular–ventricular interactions [1–5].

Table 2. Preoperative and Postoperative Echocardiographic Data[a]

Measurement	Rigid Ring	Flexible Ring
EDDI (mm)		
Preop	32.5 ± 4.3	32.8 ± 4.6
Postop	27.0 ± 2.9[b]	26.7 ± 3.4[b]
ESDI (mm)		
Preop	21.0 ± 6.0	21.4 ± 2.9
Postop	20.1 ± 4.4	18.4 ± 2.4[b]
Fraction shortening (%)		
Preop	33 ± 10	33 ± 9
Postop	26 ± 13	30 ± 9
Body surface area (m²)	1.81 ± 0.23	1.83 ± 0.19
Mitral valve area postop (cm²)	3.47 ± 1.5	2.93 ± 0.57

[a] Data are shown as the mean ± the standard deviation. [b] This represents a significant change from the preoperative value.

EDDI = end-diastolic diameter index; ESDI = end-systolic diameter index.

Table 3. Radionuclide Angiographic Data[a]

Variable	Rigid Ring	Flexible Ring
EDVI (mL/m^2)		
1	152 ± 49	159 ± 27
2	93 ± 26[b]	98 ± 19[b]
3	111 ± 49[c]	116 ± 20[c]
ESVI (mL/m^2)		
1	56 ± 28	59 ± 18
2	48 ± 24	41 ± 13[b]
3	52 ± 31	42 ± 14
EF (%)		
1	64 ± 12	63 ± 7
2	51 ± 12[b]	57 ± 13[b]
3	55 ± 12[c]	63 ± 11[c]
SBP (mm Hg)		
1	124 ± 10	125 ± 12
2	130 ± 15	140 ± 13
3	165 ± 16[c]	192 ± 25[c]
HR (beats/min)		
1	82 ± 10	80 ± 16
2	85 ± 4	80 ± 13
3	125 ± 11[c]	126 ± 26[c]
Maximum KPM		
3	654 ± 157	714 ± 129

[a] Data are shown as the mean ± the standard deviation. [b] This represents a significant change from the preoperative value. [c] This represents a significant change from the postoperative resting value.

EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; HR = heart rate; KPM = kilo · pond · meter; SBP = systolic blood pressure; 1 = preoperative values; 2 = postoperative values at rest; 3 = postoperative values at maximum exercise.

The mitral annulus changes its size and shape during the cardiac cycle [6]. Fixation of the mitral annulus with a rigid prosthesis such as an artificial mitral valve can adversely affect left ventricular function. This question was addressed more than 20 years ago by Tsakiris and associates [10], whose experimental work suggested that rigid fixation of the mitral annulus did not have a harmful effect on the left ventricle. We [2] compared the effect of rigid versus flexible mitral rings in isolated porcine hearts and could not corroborate those findings. Rather, we found that fixation of the mitral annulus with a rigid prosthesis was detrimental to systolic function of the left ventricle of pigs.

Patients with chronic mitral regurgitation secondary to myxomatous changes of the mitral valve have a dilated but contractile mitral annulus. These patients often need an annuloplasty as part of the reconstructive procedure to correct the mitral regurgitation. The annuloplasty serves to decrease the area that the leaflets have to seal, and it also allows the leaflets to coapt along several millimeters from their free margins, thus decreasing the probability of tears in areas where segments of leaflets were resected and chordae were shortened or replaced.

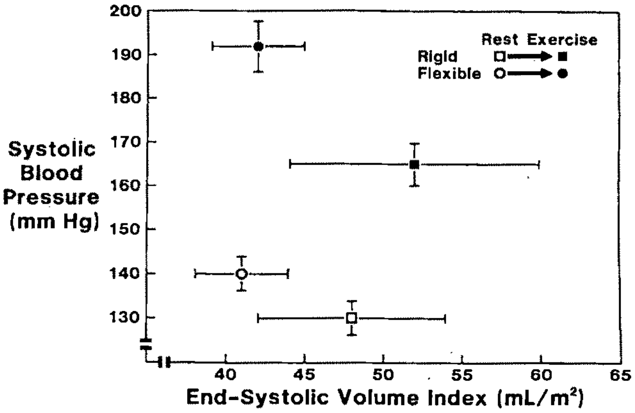

Fig 1. Left ventricular systolic function at rest and during maximum exercise as measured by pressure–volume relationships.

A number of different types of mitral annuloplasty have been employed over the years. Annuloplasty with a ring as described by Carpentier and associates [11] and, more recently, by Duran and Ubago [12], is probably the most dependable and durable of all types of annuloplasty. The Carpentier ring is rigid and remodels the mitral annulus to the size and shape of the ring [13]. The Duran ring is flexible and simply reduces the annulus to the size of the ring, allowing changes in shape during the cardiac cycle [12].

The clinical observations presented here corroborate the experimental findings that fixation of the mitral annulus with a rigid ring is more detrimental to systolic left ventricular function than fixation with a flexible ring [2]. Preoperative and postoperative mitral valve function was assessed by Doppler echocardiography, and left ventricular function was assessed by echocardiography and radionuclide angiography. The left ventricular end-diastolic dimensions and volumes decreased in both groups of patients after operation. This is usually observed in patients who have surgical correction of chronic mitral regurgitation by valve repair or valve replacement [14–16]. The end-systolic dimensions and volumes did not decrease significantly in patients with a rigid annuloplasty ring, but did so in patients with a flexible ring (see Tables

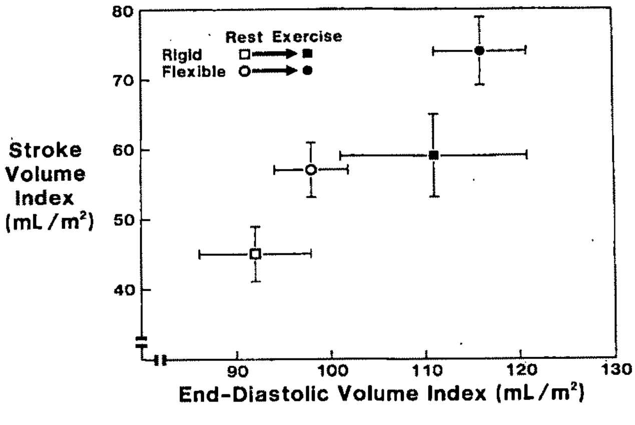

Fig 2. Left ventricular performance at rest and during maximum exercise as measured by stroke volume–end-diastolic volume relationships.

2, 3). This may be due to the fact that rigid fixation of the mitral annulus can impair the stretching and shortening of the proximal part of the basoconstrictor muscles. A very important finding was that systolic pressure–volume relationships of the left ventricle during exercise were significantly better in patients with a flexible annuloplasty ring (see Fig 1). Left ventricular performance was also better in these patients (see Fig 2).

We chose to study patients with chronic mitral regurgitation secondary to degenerative mitral valve disease because they usually have a contractile mitral annulus. We might not have shown any difference between rigid and flexible annuloplasty rings had we studied patients with rheumatic mitral regurgitation. The mitral annulus is already fairly rigid in patients with rheumatic mitral regurgitation, and fixation with a rigid or flexible ring might not seriously affect left ventricular function. The sudden alteration in the mitral annulus from a fairly contractile state to a rigid state might have an adverse effect on left ventricular function. This is perhaps the reason why fixation of the mitral annulus depresses left ventricular function in experimental animals and in patients with a normally contracting mitral annulus.

It has been documented that with time, there is an improved response of left ventricular function to mitral valve replacement [14]. We recently speculated that this might also be the case with mitral valve repair and that the results observed in this study might have been different if our postoperative hemodynamic assessments had been done longer than 2 to 3 months after operation. At the time of preparation of this report, 6 of the 25 randomized patients had a second hemodynamic assessment at 1 year postoperatively. All 6 patients demonstrated a dramatic improvement in left ventricular dimensions, volumes, and systolic function regardless of the type of annuloplasty ring used. The postoperative left ventricular function was practically normal in these 6 patients at 1 year after operation. This number of patients is too small to draw conclusions, but these results suggest that left ventricular function after mitral valve repair continues to improve beyond the second and third postoperative months and that the left ventricle may have compensatory mechanisms to overcome the problem of a rigid or flexible mitral ring as long as the mitral valve remains part of the left ventricle.

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DISCUSSION

DR DELOS M. COSGROVE (Cleveland, OH): I'd like to congratulate the authors on another important contribution to our understanding of the interaction of the left ventricle and the mitral valve on ventricular function. It was Dr David who initially renewed our interest in the contribution of the subvalvular mechanism to left ventricular function with his clinical and experimental observations. This paper adds substantially to this body of information by pointing out the importance of a flexible annulus for preservation of ventricular contractility.

While the manuscript documents the initial superior left ventricular function with the use of a flexible ring, it also alludes to two other problems associated with the use of annuloplasty rings. A smaller orifice area was calculated for patients with a flexible ring, although this did not achieve clinical or statistical significance in this particular study. This smaller valve orifice area probably results from plication of the entire annulus, including the anterior portion of the mitral annulus.

Second, Dr David had 1 case of systolic anterior motion of the anterior leaflet of the mitral valve causing left ventricular outflow tract obstruction. This has occurred in 8% of our patients with degenerative mitral valve disease who had a rigid annuloplasty ring placed as part of their valvuloplasty. This may be in part secondary to the rigid ring forcing the annulus into a euclidian plane as opposed to allowing it to assume its normal saddle-shape.

When valvuloplasty is performed, an annuloplasty ring is placed for four reasons: to correct the dilation of the annulus of the posterior portion of the leaflet, to increase leaflet coaptation, to reinforce the annular sutures, and to prevent future annular dilation.

To accomplish these functions and preserve maximum valve orifice area and ventricular function, the ideal annuloplasty ring should be universally flexible and provide a measured plication of the annulus of the posterior leaflet only. Currently, there is no annuloplasty ring that meets these requirements without compromising cardiac function.

I'd like to ask Dr David if he would speculate not only on the short-term aspect of ventricular function but on the influence of the type of annuloplasty ring on long-term ventricular function.

DR HENRY M. SPOTNITZ (New York, NY): This paper expands our understanding of the pathophysiology of surgical correction of mitral regurgitation, a clinical challenge characterized over the years by high mortality and low postoperative ejection fraction.

Laboratory investigators have identified four possible causes of adverse effects of mitral regurgitation operations on left ventricular function. The first is decreased total stroke volume through elimination of the low resistance pathway to the left atrium. The second is disruption of the papillary muscle apparatus. The third is stiffening of the normally flexible mitral annulus with a rigid prosthesis. The fourth is possible increased myocardial vulnerability, resulting in inadequate myocardial protection with standard techniques.

Clinical studies are consistent with these laboratory observations. Dr Calvin Wong and I confirmed the role of the low resistance blowoff in 1979. Dr David and his colleagues demonstrated the importance of preservation of the papillary muscle apparatus in a prior study. In the present study, they appear to have confirmed the importance of the flexible annulus. Many clinical studies, including those from our own laboratory, suggest enhanced importance of myocardial protection in these patients.

I have several questions for the authors. In connection with the issue of myocardial protection, were intraoperative studies of contractility or ejection fraction performed? Were late follow-up studies performed that might indicate continuing decrease in heart size? If so, what might be the source of restoring forces needed to decrease end-diastolic volume?

I congratulate the authors on the ongoing excellence of their clinical and physiological observations.

DR ZOHAIR AL-HALEES (Riyadh, Saudi Arabia): I congratulate Dr David for his elegant study. Let me add another advantage to the Duran ring, which at this time is a surgical advantage. This is a maneuver described by Dr Duran himself, who is currently with us at the King Faisal Specialist Hospital in Riyadh, Saudi Arabia.

We perform the ring annuloplasty but do not tie down the sutures. Instead, we bring the ring down and hold it with three tourniquets and check for competence. If the repair is satisfactory, we tie the sutures. If the repair is totally unsatisfactory, then we remove the valve and replace it. Up until this point you can do the same with a Carpentier ring, but if you discover a problem with the subvalvular apparatus, then there is an advantage for the Duran ring.

At this stage you can split the ring in half and bring it up away from the valve, and that would make the exposure very good, allowing easy access for performing the subvalvular repair. We have found this maneuver very helpful, and it can be utilized whenever there is doubt about the repair to save time.

Another advantage for the flexible annuloplasty ring is that you can still perform commissuroplasty even while the ring is in place.

A question that one might think about is whether the ring remains flexible after implantation. A ring explanted 5 years after implantation remained flexible, which proves the fact.

It is important to point out the changes in the shape of the mitral valve in systole and diastole with both Carpentier and Duran rings in place. With the Carpentier ring, the shape of the valve remains rigid and unchanged between systole and diastole, whereas with the flexible Duran annuloplasty ring, the valve can take the shape of the normal mitral valve in systole.

These advantages and what Dr David discussed in his paper make us firmly believe in the excellent results achieved in mitral valve repair utilizing the flexible Duran ring.

DR DAVID: I would like to thank Drs Cosgrove, Spotnitz, and Al-Halees for their comments. I will try to answer their questions.

I do not have a good explanation why the postoperative Doppler studies showed a slightly larger mitral orifice in patients with a rigid annuloplasty ring. I should emphasize that the difference did not reach significance. Although pursestring suture of the mitral annulus is possible during the insertion of a Duran ring, I do not believe this is the explanation in our cases. We secure this type of ring with a running suture that is passed through the mitral annulus and around the ring. We found that this technique minimizes the possibility of this complication. We secure the Carpentier ring with interrupted sutures.

There is indeed a temporal response of the left ventricular function after mitral valve reconstruction. The results presented in this study are those we obtained 2 to 3 months after operation. A small number of patients had their ventricular function reassessed at 1 year after operation and they were amazingly normal, regardless of the type of ring. I am committed to continue investigating this phenomenon and shall report the results to you in the future.

I have to admit that I am somewhat casual with myocardial protection during short operations. Mitral valve reconstruction can usually be done within 35 to 40 minutes and I use a little more than 1 L of cold blood cardioplegia in one or two shots and systemic hypothermia of 30°C. None of the patients in this study had electrocardiographic or enzymatic evidence of myocardial infarction.

Predonated Autologous Blood Use in Elective Cardiac Surgery

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The risks of homologous blood transfusion are well documented and recently increased with the emergence of acquired immunodeficiency syndrome. Preoperative autologous donation has been suggested to reduce these risks. This is a report concerning 104 consecutive adult autologous donors (group 1) who had an elective cardiac operation. A similar group of 111 patients operated on during the same period but without autologous blood donation was used for comparison (group 2). Both groups contained similar numbers of patients with coronary artery disease, valvular disease, and mixed lesions, and both had several patients with atrial septal defects. Group 2 patients (mean age, 67.8 years) were significantly older than group 1 patients (mean age, 58.9 years) ($p < 0.05$). The mean donation in group 1 was 4.1 units, but 12 (11.5%) had to discontinue donations. Increasing angina in 10 (12.2%) of the 82 patients with coronary artery disease was the most common complication, and necessitated hospitalization in two instances. In 77 (75.5%) of the 102 group 1 patients who had operation and 23 (21%) of the 110 group 2 patients, no homologous blood products were required. Group 1 patients used significantly less homologous fresh frozen plasma (0.1 unit versus 0.97 unit; $p < 0.005$) and packed red blood cells (0.6 unit versus 2.1 units; $p < 0.001$) than group 2 patients. Group 1 patients received 3.3 and 3.1 units of autologous packed cells and plasma, respectively. No complications of autologous transfusion were seen. Predonation of autologous blood is an effective, safe method of reducing homologous blood requirements in elective cardiac operations, but it does carry some risk, especially in patients with coronary artery disease.

(Ann Thorac Surg 1989;47:529–32)

Since the inception of cardiac operations done with cardiopulmonary bypass, multiple advances and innovative techniques have allowed a marked reduction in the use of blood products. These include the use of crystalloid prime for extracorporeal circulation as well as techniques for returning the patient's red cells during the operative and postoperative periods. In spite of these advances, the requirement for banked blood products persists. Although the requirement for transfusion has been reported to be as low as 1 to 2 units per patient [1], this still carries major risks, including transfusion reaction and transmission of hepatitis, acquired immunodeficiency syndrome, and bacterial sepsis [2–10]. Such risks have stimulated recent interest in the use of autologous blood in cardiac procedures. Autologous blood can be obtained in the operating room immediately before the institution of cardiopulmonary bypass or through donation during the preadmission period. This blood can then be stored until it is needed.

The concept of autotransfusion was originally reported in the 1800s [11]. The first thoracic surgical application was not until 1917 and involved the treatment of massive hemothorax [12]. Grant [13] was among the first to describe the predonation and storage of autologous blood for an elective surgical procedure. There have been several reports [14–18] demonstrating the safety and efficacy of predonation of autologous blood in cardiac surgical patients. In 1987, we embarked on a policy of offering predonation of autologous blood to elective cardiac surgical patients weighing 40 kg or more and aged 12 years or older. This study reports our experience with the first 104 consecutive autologous blood donors.

Material and Methods

The patients studied were all operated on at the Albany Medical Center Hospital between March and August 1987. Group 1 consisted of 104 consecutive patients who chose autologous blood donation. A similar group of 111 patients having operation during this same period without autologous blood donation was used for comparison (group 2). The patients were on an elective waiting list of 4 to 7 weeks. Patients requiring emergency cardiac operations were excluded. Surgical procedures included coronary artery bypass grafting and valve replacement or repair with or without coronary artery bypass grafting. Several patients with atrial septal defects were included.

The patients in group 1 donated an average of 4.1 units of autologous blood (range, 1 to 6 units) at a rate of 1 unit per week. This blood collection was performed primarily at the Albany Medical Center Hospital, although a satel-

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lite program was set up at one community hospital in the area. Donations were carried out by and in accordance with standards set by the American Red Cross Blood Services. The blood was separated into its components of plasma, which was frozen, and packed red blood cells, which were stored in ADSOL red cell preservative (Fenwal Laboratories, Deerfield, IL). If the anticipated storage period was to be greater than 42 days, the red cell portion of each unit was frozen.

All autologous donors were given 324 mg of ferrous sulfate three times daily. No patient was allowed to donate when the initial hematocrit was less than 34%. All patients had antiplatelet medications discontinued from seven to ten days before operation. A careful history regarding prior bleeding problems was taken. Laboratory evaluation including prothrombin time, partial thromboplastin time, and platelet count was also done preoperatively.

Autologous blood collection at the onset of cardiopulmonary bypass was carried out by connecting two Fenwal CPDA-1 blood collection bags to a Y connector in the venous line of the cardiopulmonary bypass circuit. At the initiation of cardiopulmonary bypass, venous blood was initially drained into the blood collection bags while arterial transfusion maintained systemic arterial pressure. Approximately 30 seconds was required to draw from 800 to 1,200 mL of whole blood. This was carried out in all patients whose initial hematocrit before bypass was 28% or greater, thus resulting in an initial hematocrit of 18% or greater after bypass.

The heparin in the collected blood was neutralized with 30 mg of protamine sulfate before its reinfusion into the patient at the cessation of cardiopulmonary bypass and after protamine reversal of systemic heparinization. Our postoperative transfusion protocol allowed hematocrit to drop to 25% or less before transfusion. Platelets and fresh frozen plasma were transfused only as coagulopathies were encountered. There was no routine transfusion of blood products. For patients who had predonated autologous blood, an attempt was made to return all of their packed red cells and fresh frozen plasma. Volume requirements were met by the use of crystalloid and 5% albumin solution.

Cardiopulmonary bypass was carried out using a crystalloid prime and COBE Optiflo II bubble oxygenator (COBE Laboratories, Inc, Lakewood, CO). At the completion of cardiopulmonary bypass, heparinization was reversed using protamine titrated to activated clotting times as well as Hepcon (HemoTec, Inc, Englewood, CO) determinations of circulating heparin. Blood conservation techniques utilized in all patients included the return of all blood from the pump oxygenator and autotransfusion of intraoperative blood loss.

Statistical analysis was carried out using Student's *t* test and Fisher's exact test.

Table 1. Group Comparison

Variable	Group 1	Group 2	*p* Value
Mean age (yr)	58.9	63.8	<0.05
Mean cardiopulmonary bypass time (min)	134	132	NS
Mean chest tube drainage (mL)	611	699	NS
Mean ejection fraction	0.59	0.56	NS
Mean no. of grafts per patient	4.1	3.9	NS

NS = not significant.

Table 2. Procedures Performed

Procedure	Group 1	Group 2
Coronary artery bypass grafting	78	86
Valve replacement or repair with or without coronary artery bypass grafting	19	23
Atrial septal defect repair	5	1

Results

There was no significant difference in total cardiopulmonary bypass time, volume of postoperative chest drainage, or number of grafts per patient between groups 1 and 2. There was a significant difference in age, group 1 being younger than group 2 (Table 1). The procedures performed were similar in each group (Table 2). One patient in group 1 and 2 patients in group 2 had undergone a previous cardiac procedure. An average of 4.1 units of blood was predonated by patients in group 1 over a period of approximately 28 days. The average admission hematocrit was significantly lower in group 1 than in group 2, and the average discharge hematocrit was significantly higher in group 1 (Table 3). This can be explained by the return of all predonated packed red blood cells to patients in this group.

Seventy-seven (76%) of the 102 patients in group 1 who underwent operation required no homologous blood products. In group 2, only 23 (21%) of 110 patients were managed without any homologous blood products. In group 1, patients received an average of 3.3 units of autologous packed cells and 3.1 units of autologous plasma. The homologous blood product requirements are summarized in Table 4. There were no complications of either autologous or homologous blood product transfusion.

Twelve (12%) of the 104 patients in the autologous donation group had to discontinue donations. The most

Table 3. Hematocrit Comparison

Hematocrit	Group 1	Group 2	*p* Value
Admission			
Range (%)	26–46	30–49	
Mean (%)	36.6	39.4	<0.001
Discharge			
Range (%)	24–49	25–40	
Mean (%)	34.4	32.2	<0.001

Table 4. Homologous Blood Product Usage

Product	Group 1	Group 2	*p* Value
Fresh frozen plasma (average units/patient)	0.1	0.97	<0.005
Packed red blood cells (average units/patient)	0.6	2.1	<0.001

common reason was increasing angina in patients with coronary artery disease. This occurred in 10 (12%) of the 82 patients in whom the primary diagnosis was coronary artery disease. Hospitalization was required for 2 of these patients because of increasing anginal pain. The other 2 patients had to discontinue donations because of anemia with hematocrit less than 34%. Four patients required an earlier surgical date because they experienced increasing symptoms during the donation period. Homologous as well as autologous transfusions were required for 2 of these 4 patients.

During this same period, an equal number of patients (4) not donating autologous blood had a change in status from elective to urgent operation, thus necessitating an earlier surgical date. There were 2 patients in the autologous donation program and 1 patient in group 2 who died during the preoperative period (p = not significant). One patient in group 2 who underwent aortic and mitral valve replacement with a prolonged cardiopulmonary bypass time (197 minutes) required reoperation for bleeding. This patient had a coagulopathy postoperatively, which required plasma and platelet transfusions for correction. No patient in group 1 required reoperation.

Comment

Current blood conservation techniques have been quite successful in avoiding the crisis in blood banking that was feared because of the geometric increase in cardiac operations over the past 10 to 15 years. Several studies [19–22] have shown a decrease in the number of units used per patient in cardiac operations. This has been accomplished by a multitude of techniques, including storing autologous blood taken immediately preoperatively [19–27] and accepting lower hematocrit levels postoperatively [20–22]. It has been shown that predonated autologous blood decreases the homologous transfusion requirements and is safe in a wide variety of elective surgical procedures including cardiac procedures [15, 18, 27, 28].

The risk of major transfusion complications including non-A, non-B hepatitis, acquired immunodeficiency syndrome, and the more acute incompatibility reactions, febrile reactions, and allergic reactions are reduced by lessening exposure to transfusion. We found a marked increase in the number of patients who were able to undergo cardiac operation without any homologous blood products when a predonation program was practiced.

Patients with severe coronary artery disease are at risk for the development of increasing symptoms and the need to terminate their predonation program. We did not find, however, that this increase in symptoms requiring a change in the timing of operation was related to participation in a predonation program.

We conclude that predonation of autologous blood in patients scheduled for an elective cardiac procedure, including patients with severe coronary artery disease, is a safe and effective method to decrease homologous blood requirements. Patients with severe coronary artery disease are at risk for experiencing increasing symptoms during the preoperative delay required for donation. This risk does not appear to be associated with the predonation process. Problems encountered in the preoperative period can be minimized by close monitoring and acceleration of the surgical date when necessary.

We thank David McCloskey, Frank Strickler, Judy Baker, and Phyllis Nantista for help in collecting data and Patricia Novak for her assistance in the preparation of this manuscript.

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DISCUSSION

DR ROBERT L. THURER (Boston, MA): At our 1979 meeting, I presented a study showing that 94% of patients having elective coronary artery bypass grafting could be successfully operated on without the use of banked blood if intraoperative and postoperative salvage were coupled with hemodilution and the avoidance of prophylactic transfusion [20]. At that time, predeposit autologous donation was not practiced because of logistical difficulties. During the past decade, the increasing complexity of so-called routine cardiac operations, along with the increased age and debility of the patients, has resulted in a continued need for blood transfusion. This need, as well as the increased awareness of transfusion-transmitted diseases, has stimulated the use of predeposit autologous donation for cardiac surgical patients.

Dr Britton's study provides further evidence that cardiac surgical patients can safely donate blood for their own use and that this method can reduce exposure to homologous blood. Several questions, however, are still unanswered.

First, do the donations render patients anemic at the time of operation or do the patients restore their depleted red cell mass before operation? This study suggests that patients who predonate go to the operating room with lower hematocrits and receive more total transfusions, autologous and homologous. In a similar group at Boston's Beth Israel Hospital, however, my colleagues and I found that preoperative hematocrits were not reduced and total transfusions not increased. We believe patients should be given time to restore their red cell mass before operation.

Second, there is debate about when to transfuse autologous blood. Because it is safer than bank blood, Dr Britton's group and others transfuse it liberally. On the other hand, even its small risks should not be ignored.

Finally, are donations by cardiac surgical patients truly safe? In this study, 12% of patients had to discontinue donating because of increasing angina. Two patients died during the period of blood collection. In our experience, 1 patient required hospitalization for increasing angina. These findings are not significantly different from those in the control groups, but we should remember that although frequent and serious, the complications of banked blood are only rarely life threatening. I believe these donations are safe in properly selected patients; however, the fact that the total reported experience is still small forces us to continue to look at such donations critically.

The main hazard of homologous transfusion is non-A, non-B hepatitis. This peaks at about ten donor exposures. Therefore, a saving of one or two exposures in a patient receiving few units results in a greater risk reduction than do larger savings in patients exposed to many donors. Attention to all aspects of blood conservation will thus result in a substantial risk reduction even though each method may account for only a small amount of saved blood.

I enjoyed Dr Britton's presentation and the opportunity to read the manuscript. I am concerned about the validity of the control group and also the fact that the mean discharge hematocrits in both groups were greater than 32%, perhaps representing excessive transfusion.

In closing, I request that Dr Britton tell us more about the patient selection criteria, especially as they relate to donor safety. Also, does he really believe the transfusion of fresh frozen plasma is necessary, as the autologous patients who received it bled the same amount as the control patients who did not?

DR BRITTON: I thank Dr Thurer for his kind comments. In regard to the patient selection criteria, the selection was made by the referring cardiologist. The number of patients in both groups with left main trunk disease was not significantly different. The severity of disease, as judged by ventricular function and the number of grafts per patient, was similar between the two groups.

In regard to the hematocrits at the time of discharge, transfusions were not carried out in the group 2 patients if the hematocrit was greater than 25%. We did believe, because of the safety of autologous transfusion, that patients in the autologous group should receive all of the blood that they had predonated, if possible. The fresh frozen plasma was also given in the autologous group as volume replacement. As Dr Thurer points out, this did not seem to make a difference in the amount of postoperative blood loss. In group 2, fresh frozen plasma was given only to patients who demonstrated a coagulopathy.

When Should the Hypoplastic Right Ventricle Be Used in a Fontan Operation? An Experimental and Clinical Correlation

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Eight anesthetized dogs underwent closure of the tricuspid valve and a Fontan procedure, and the right ventricular cavity was reduced in stepwise fashion. There was an increase in right atrial pressure from 9.3 ± 2.2 to 14.1 ± 2.4 mm Hg ($p < 0.001$), a decrease in pulmonary artery pulse pressure from 10.8 ± 2.2 to 6.8 ± 2.2 mm Hg ($p < 0.01$), and a decrease in cardiac index from 2.7 ± 0.3 to 2.2 ± 0.2 L/min/m^2 ($p < 0.001$) when the ventricular size was dropped from 50% to 25% of normal. The difference between mean pulmonary artery pressure and mean right atrial pressure, which reflects the positive stroke work index of the ventricle, disappeared once the right ventricular cavity was reduced to 25% of normal (15.0 ± 6.1 versus 14.1 ± 2.4 mm Hg; p = not significant). Experimental results were correlated with postoperative catheterization data from 19 patients with tricuspid atresia who had the Fontan operation. Mean right atrial pressure was 18 ± 4.6 mm Hg and cardiac index was 2.35 ± 0.65 L/min/m^2 in patients with a direct atrium–pulmonary artery anastomosis or an atrioventricular anastomosis with a right ventricular cavity less than 30% of normal versus 13 ± 3.2 mm Hg and 3.42 ± 0.46 L/min/m^2 for those with an atrioventricular connection and a right ventricular cavity greater than 30% of normal ($p < 0.05$ and $p < 0.02$, respectively). The right ventricle enlarged from 27% ± 6% of normal preoperatively to 35% ± 10% of normal on follow-up ($p < 0.05$). Left ventricular ejection fraction was 90% ± 11% of normal in patients with an atriopulmonary anastomosis and 104% ± 16% of normal in those with an atrioventricular connection ($p < 0.05$). Findings suggest that a right ventricular size that is 30% of normal or less does not contribute to cardiac output or positive stroke work, whereas a right ventricular size greater than 30% of normal increases stroke volume, decreases systemic venous hypertension, and improves left ventricular function.

(Ann Thorac Surg 1989;47:533–8)

Among the important factors that contribute to subnormal cardiac output at rest and during exercise after the Fontan operation with direct atrium–pulmonary artery anastomosis is the absence of the right ventricle [1–3]. Several studies have demonstrated that even in anatomically normal hearts, right ventricular function is an important determinant of maximal oxygen consumption when left ventricular abnormalities are present. Hence, to optimize short-term and long-term functional results, every attempt should be made to utilize the subpulmonary ventricle in the Fontan procedure by performing a valved atrioventricular connection. Because these ventricles vary considerably in size, it is often difficult to determine the "appropriate" size of right ventricle that will provide hemodynamic benefits that outweigh the drawbacks of prosthetic valve insertion necessitated by its use.

This report aims at determining the right ventricular size or sizes that could increase the cardiac output when incorporated into the Fontan operation. It attempts to define the small, "functionally useless" ventricular chamber that should be bypassed in favor of a direct right atrium–pulmonary artery anastomosis. The study consists of an experimental part, which evaluates the acute hemodynamic changes that result from a decrease in right ventricular size after the Fontan procedure, and a clinical part in which these hemodynamic variables are reviewed in patients with different subpulmonary ventricular sizes who had a Fontan operation.

Material and Methods

Experimental Part

Eight mongrel dogs weighing 7.2 to 9.1 kg were used. Through a median sternotomy, the anesthetized animals were cannulated and started on normothermic cardiopulmonary bypass. The right atrium was opened, and the tricuspid valve was closed with a polytetrafluoroethylene patch secured in place with multiple interrupted sutures (Fig 1A). A ventriculotomy was made in the outflow tract of the right ventricle, and a pedicle of atrial wall was anastomosed to the ventriculotomy lip (Fig 1B). A 21-mm

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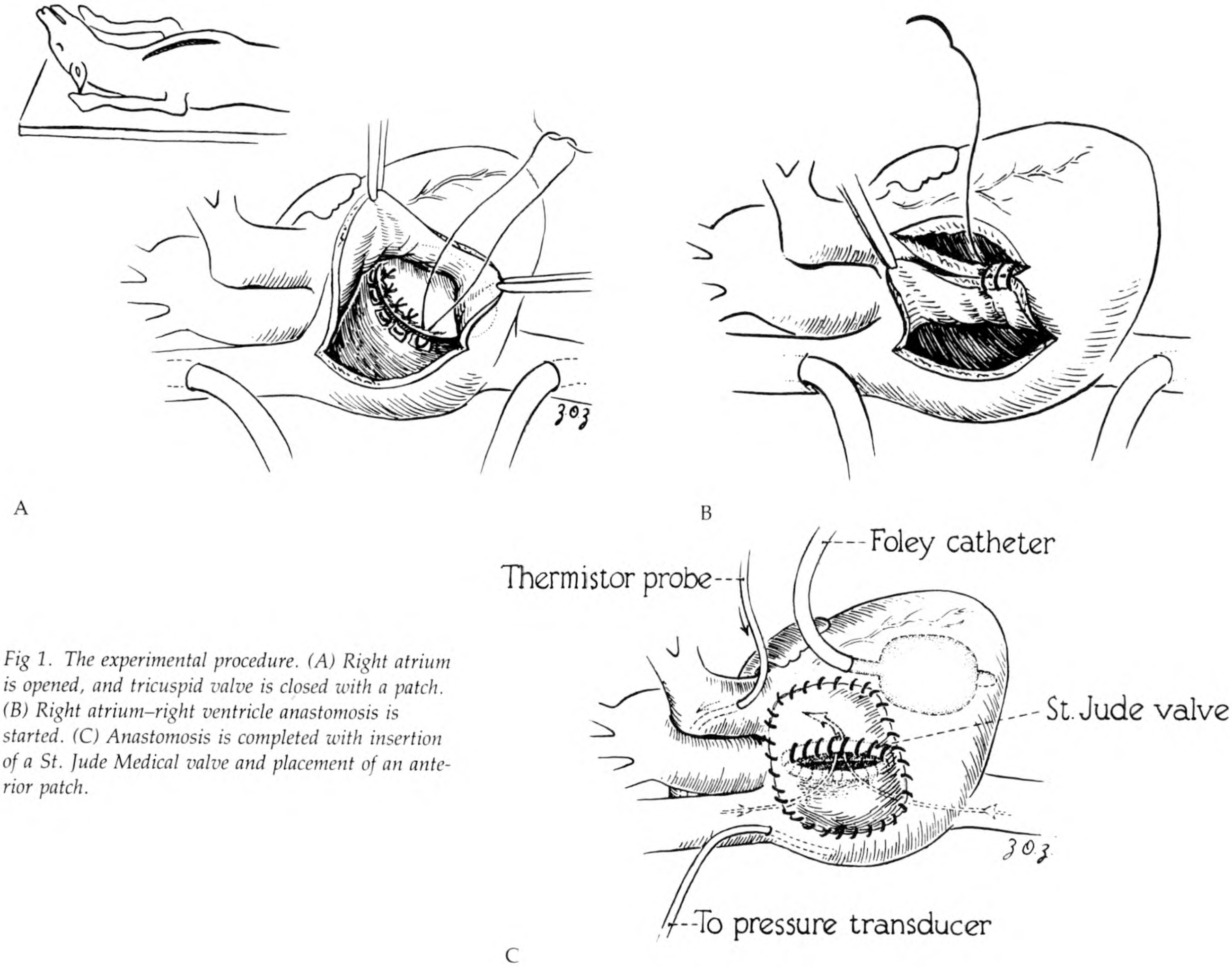

Fig 1. The experimental procedure. (A) Right atrium is opened, and tricuspid valve is closed with a patch. (B) Right atrium–right ventricle anastomosis is started. (C) Anastomosis is completed with insertion of a St. Jude Medical valve and placement of an anterior patch.

St. Jude Medical mitral valve was inserted at the atrioventricular junction, and the anastomosis was completed anteriorly with a large patch (Fig 1C). A catheter leading to a pressure transducer and a thermistor probe were inserted in the right atrium and pulmonary artery, respectively, and a Foley catheter with a 30-mL balloon was introduced into the apex of the right ventricle. Cardiopulmonary bypass was then discontinued, and the dogs were allowed to stabilize for 15 minutes. Blood gases and electrolytes were checked at the end of bypass.

Baseline data consisting of right atrial pressures (systolic, diastolic, and mean), pulmonary artery pressures (systolic, diastolic, and mean), and cardiac output were collected. The right ventricular size was then reduced in a stepwise fashion to 75%, 50%, 25%, and 0% of normal by inflating the Foley catheter balloon with the appropriate volume of saline solution. Data collection was repeated with each right ventricular size with and without continuous infusion of epinephrine at 0.05 μg/kg/min.

The dogs were killed at the end of the procedure. The integrity of the tricuspid valve closure and the patency of the Fontan anastomosis were checked. All animals were treated humanely in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Clinical Part

Postoperative catheterization results from 19 patients who underwent the Fontan operation for tricuspid atresia and normally related great vessels were reviewed. Data collection included right atrial pressures (systolic, diastolic, and mean), pulmonary artery pressures (systolic, diastolic, and mean), cardiac index, left ventricular ejection fraction, and right ventricular size. Ten patients were type Ia, and all had a right atrium–main pulmonary artery anastomosis. The remaining 9 patients were type Ib or Ic and had a right atrium–right ventricle anastomosis. A porcine valve was used in all patients with an atrioventricular connection and in 50% of patients (5/10) with an atriopulmonary anastomosis.

Cardiac index was calculated using the Fick principle. Right and left ventricular volumes and ejection fractions were estimated from biplane angiograms using computerized planimetry as suggested by Lange and colleagues [4].

All data were analyzed and compared using Student's t test. A p value of 0.05 or less was considered significant.

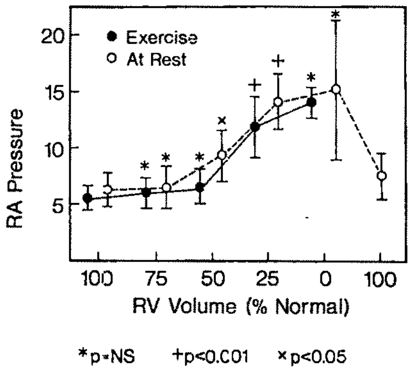

Fig 2. Changes in right atrial pressure (in mm Hg) in response to reduction in right ventricular size. Exercise indicates continuous epinephrine drip. (NS = not significant; RA = right atrial; RV = right ventricular.)

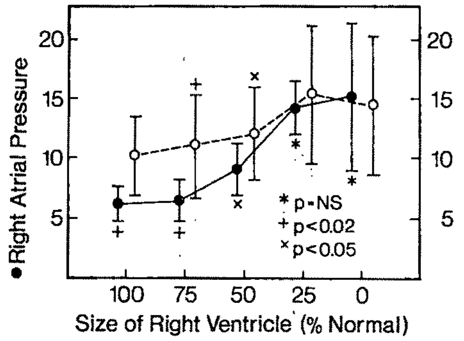

Fig 4. Positive stroke work index of right ventricle, namely, the difference between mean pulmonary artery (PA) pressure (in mm Hg) and mean right atrial pressure (in mm Hg), decreases gradually in response to obliteration of right ventricular cavity. (NS = not significant.)

Results

Experimental

RIGHT ATRIAL PRESSURE. There was a progressive increase in mean right atrial pressure as the right ventricular volume decreased in size (Fig 2). The change became significant when the ventricular size was decreased to 50% of normal (9.3 ± 2.2 versus 6.5 ± 1.7 mm Hg; $p < 0.05$) and showed a further increase when the ventricular size reached 25% of normal (9.3 ± 2.2 versus 14.1 ± 2.4 mm Hg; $p < 0.001$), but remained unchanged (15.1 ± 6.2 mm Hg; p = not significant) when the ventricle was totally excluded (0% of normal volume). A similar trend was observed during continuous epinephrine drip.

PULMONARY ARTERY PRESSURE. Pulmonary artery pulse pressure showed a progressive decrease as right ventricular volume was reduced (Fig 3). The change became significant when ventricular volume reached 25% of normal (6.8 ± 2.2 mm Hg at 25% versus 10.8 ± 2.2 mm Hg at 50%; $p < 0.01$). Similar changes were noted during epinephrine infusion.

RIGHT VENTRICULAR POSITIVE STROKE WORK INDEX. The difference between mean pulmonary artery pressure and mean right atrial pressure, which is a reflection of the positive stroke work index of the right ventricle, decreased gradually as the ventricle was reduced in size (Fig 4). No ventricular positive work was produced once the ventricular size reached 25% of normal (15.0 ± 6.1 versus 14.1 ± 2.4 mm Hg; p = not significant).

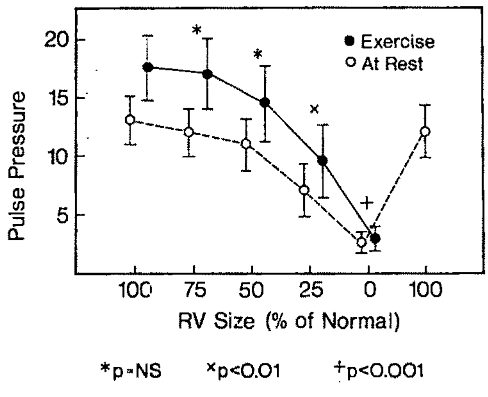

Fig 3. Changes in pulmonary artery pulse pressure (in mm Hg) in relation to size of right ventricle. (NS = not significant; RV = right ventricular.)

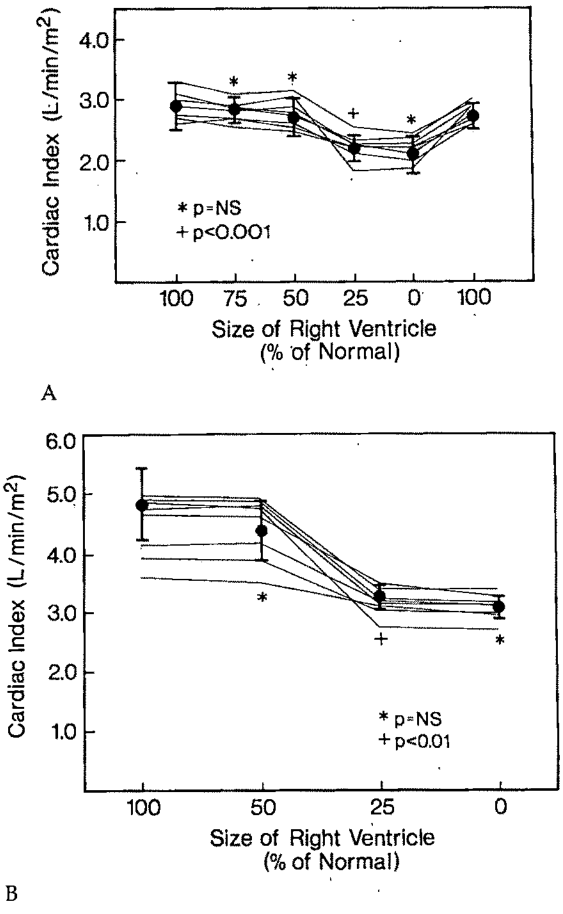

Fig 5. Response of cardiac index to changes in right ventricular size (A) at rest and (B) during exercise (epinephrine infusion). (NS = not significant.)

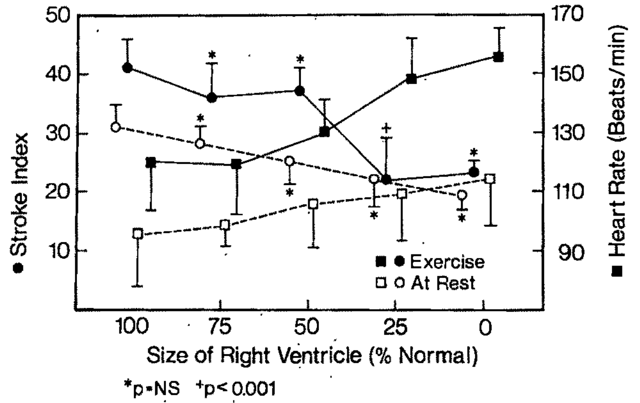

Fig 6. Changes in stroke volume index (in mL/m²) and heart rate after reduction in right ventricular size. (NS = not significant.)

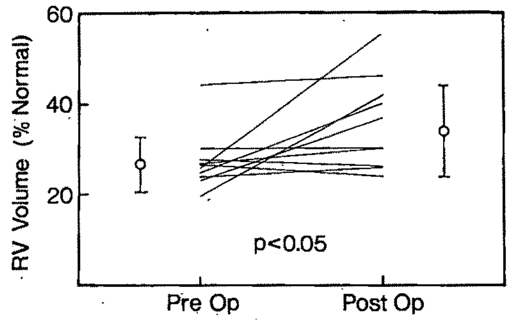

Fig 8. Changes in right ventricular (RV) size after Fontan operation.

CARDIAC INDEX AND STROKE VOLUME INDEX. The decrease in cardiac index became significant when the functional volume of the right ventricle dropped to 25% of normal (2.2 ± 0.2 versus 2.7 ± 0.3 L/min/m²; $p < 0.001$) (Fig 5A). Further reduction in ventricular volume did not affect the cardiac index (2.1 ± 0.3 versus 2.2 ± 0.2 L/min/m²; p = not significant). Similar results were obtained during epinephrine administration (Fig 5B). Analysis of changes in stroke volume index at rest revealed a tendency toward smaller volumes when the right ventricular cavity was decreased in size (Fig 6). This trend became more apparent during epinephrine infusion; there was a significant drop in stroke volume index ($p < 0.001$) and a corresponding significant rise in heart rate ($p < 0.05$) once the ventricular size was decreased from 50% to 25% of normal.

Clinical

Mean right atrial pressure was 18 ± 4.6 mm Hg in patients with an atriopulmonary connection and patients with an atrioventricular connection in whom the right ventricle was less than 30% of normal and 13 ± 3.2 mm Hg in patients with an atrioventricular anastomosis in whom the right ventricle was greater than 30% of normal ($p < 0.05$) (Fig 7). Enlargement of the hypoplastic right ventricle occurred in the majority of patients (27% ± 6% of normal preoperatively to 35% ± 10% of normal postoperatively; $p < 0.05$) (Fig 8). Cardiac index at rest was 2.35 ± 0.65 L/min/m² for patients with a direct right atrium–pulmonary artery anastomosis and 2.27 ± 0.36 L/min/m² for patients with an atrioventricular anastomosis when the right ventricular size was 30% of normal or less (p = not significant). In contrast, cardiac index was 3.42 ± 0.46 L/min/m² in patients whose right ventricle was larger than 30% of normal ($p < 0.02$) (Fig 9). Left ventricular ejection fraction was 90% ± 11% of normal in patients with a direct atrium–pulmonary artery anastomosis and 104% ± 16% of normal in patients with an atrioventricular connection and a right ventricle greater than 30% of normal ($p < 0.05$) (Fig 10).

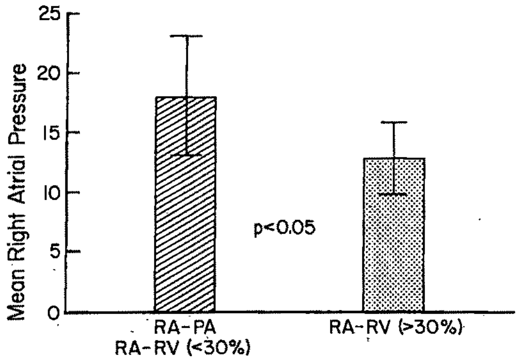

Fig 7. Mean right atrial pressure (in mm Hg) in patients with atriopulmonary anastomosis versus those with atrioventricular connection. (RA–PA = right atrium–pulmonary artery anastomosis; RA–RV = right atrium–right ventricle anastomosis.)

Comment

Better postoperative results and long-term functional performance have been achieved with the Fontan operation when an atrioventricular rather than an atriopulmonary anastomosis is made [5]. Fontan and associates [6] have demonstrated that use of the right ventricle and atrioventricular homograft conduits has yielded a better postoperative functional class, a lower right atrial pressure, and an improved left ventricular ejection fraction. Similarly, Bull and colleagues [7] found that in patients with good right ventricular size, positive stroke work was evident

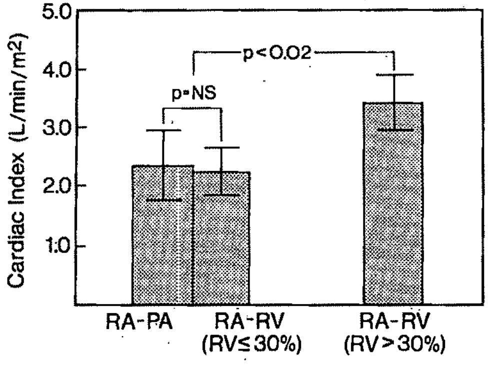

Fig 9. Comparison of cardiac index between patients with atrioventricular connection and those with atriopulmonary connection. (NS = not significant; RA–PA = right atrium–pulmonary artery anastomosis; RA–RV = right atrium–right ventricle anastomosis; RV = right ventricle.)

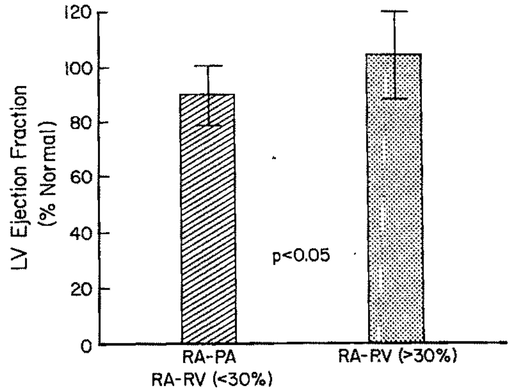

Fig 10. Relationship of left ventricular (LV) *ejection fraction to size of right ventricle in patients with Fontan procedure.* (RA–PA = *right atrium–pulmonary artery anastomosis;* RA–RV = *right atrium–right ventricle anastomosis.)*

when an atrioventricular connection with a valved conduit was performed. A recent study by Coles and associates [8] revealed a survival advantage for patients having a Fontan operation that makes use of the residual right ventricle, and demonstrated incremental stroke work attributable to this ventricle.

Use of the small right ventricle should be accompanied by insertion of a right atrioventricular valve to prevent regurgitation into the systemic venous bed, and therefore should provide enough improvement in hemodynamics to offset the long-term complications of prosthetic valves [6, 9]. To achieve this goal, the ventricle should be large enough to provide pulsatile pulmonary blood flow, contribute to positive stroke work, and preserve the Starling effect during exercise and stress. This experimental study demonstrates that a right ventricular size of 25% to 30% of normal does not contribute significantly to cardiac output and is better excluded from the circulation to avoid the need for valve insertion. Similarly, the clinical data suggest that the subpulmonary ventricle should be at least 30% of normal size before it can provide an increase in systemic cardiac output. The work of Coles and colleagues [8] supports these findings. In their report, positive right ventricular stroke work was appreciable only when the size ratio of the right ventricle to the left ventricle was 0.3 or more.

Another advantage of using the right ventricle in the Fontan operation that became apparent from this work is the reduction in mean right atrial pressure. Ventricular sizes of more than 30% of normal were associated with significant reduction in right atrial hypertension, both at rest and during exercise. These results confirm the data of Bull and associates [7], and imply that patients who are expected to have high postoperative right atrial pressure because the pulmonary vascular bed is not optimal for the Fontan procedure, such as the patient with small pulmonary arteries or slightly elevated pulmonary vascular resistance, would benefit from incorporating a functional right ventricle. The data also indicate that in patients with tricuspid atresia and complete transposition of the great arteries who have previous pulmonary artery banding or subaortic obstruction, it is justifiable to perform an arterial switch operation concomitant with the Fontan operation to make use of the good-sized right ventricle because these patients fare poorly after an isolated Fontan repair [10].

Impaired exercise response of patients who have had the Fontan operation has been documented by several studies and is due to the absence of a functional right ventricle [3, 11, 12]. In the experimental animals, the increase in cardiac output during epinephrine infusion resulted from an increase in heart rate when the ventricular cavity was less than 30% of normal size, thus indicating that patients with a direct atrium–pulmonary artery connection are incapable of increasing the stroke volume during exercise [13, 14]. Incorporation of a good-sized right ventricle (greater than 30% of normal) resulted in improvement in exercise performance and stroke volume. Although the hemodynamic effects observed in the experimental animals during infusion of epinephrine might not be identical to those seen during exercise in humans, the similarities are close enough to allow a valid comparison.

The mechanisms by which the right ventricle contributes to improved cardiac output seem to be related to improved filling of the left side of the circulation and, more importantly, augmentation of left ventricular function [13, 15]. Patients with a good-sized right ventricle had better left ventricular ejection fraction than those with a direct atriopulmonary connection, a finding that supports the previously proven role of the right ventricle in the dynamics of left ventricular contractions [15].

The potential for right ventricular growth after an atrioventricular Fontan connection has not been completely studied [16]. Although there was an overall increase (8%) in right ventricular size in our patients, the trend is inconsistent and is subject to inherent error in measuring ventricular size with a patch in place. It seems from reviewing the cases of these patients that ventricles with trabecular portions are likely to enlarge after incorporation into the Fontan operation. However, a larger number of patients might be needed to evaluate objectively the postoperative growth pattern of these ventricles.

The reported frequent obstruction of Dacron conduits placed between the atrium and the ventricle for the Fontan operation [9] can be minimized by direct atrioventricular anastomosis using a pedicle of atrial tissue posteriorly and a large polytetrafluoroethylene patch anteriorly [17]. This type of connection has the added advantage of conforming to the space available and decreasing the chances of sternal compression. None of our patients thus treated experienced anastomotic stenosis.

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Important Notice From The Society of Thoracic Surgeons

Annual Meeting Changes

After extensive deliberation, the Council voted unanimously to return the time of the annual meeting to the January–February period beginning in 1991. The following dates and places have been selected by the Council.

25th Annual Meeting
September 11–13, 1989
Baltimore, Maryland

Interim Meeting
September 22–23, 1990
Chicago, Illinois

26th Annual Meeting
February 18–20, 1991
San Francisco, California

The interim meeting of September 22–23, 1990, will resemble that of the very successful interim meeting held in Dallas, Texas, January 30–February 1, 1987. Many members have requested that this format be repeated. In addition to its scientific component, this meeting will emphasize the socioeconomic aspects of cardiothoracic surgical practice, issues that currently require extensive time and effort by the Council and committees of The Society. The 26th Annual Meeting in February 1991 will have the usual annual meeting format.

The Value of Protective Isolation Procedures in Cardiac Allograft Recipients

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The impact of protective isolation on the incidence of infection in 60 cardiac transplant recipients (mean age, 49.2 years) was studied in a prospective randomized trial. Thirty patients were randomized to protective isolation, which consisted of private room, hat, mask, sterile gown, and handwashing. Thirty patients were randomized to no isolation, which meant they recovered in a crowded, open intensive care unit and were adjacent to recipients of liver transplants or patients who were on the trauma, neurosurgical, and general surgical services, many of whom had an infection of the incision or a pulmonary infection. There was no difference between groups in the proportion of patients in whom infection developed ($\chi^2[1] = 0.27$; $p = 0.6$), the number of infection-related deaths (2 in each group), the types of infection (bacterial, viral, fungal, or protozoal), or the overall outcome. Because protective isolation offered no benefit over standard care in protecting these patients from infections or the associated complications, we have discontinued its routine use after cardiac transplantation.

(Ann Thorac Surg 1989;47:539–45)

Cardiac transplantation is an accepted method of therapy for end-stage heart disease [1]. The actuarial survival for patients who have undergone orthotopic heart transplantation approaches 80% at 1 year, and the actuarial 5-year survival is between 50% and 60% [1–6]. Improved survival after cardiac transplantation has been attributed to advances in retrieval and preservation of donor hearts [7], better immunosuppression based on cyclosporine [8], earlier and improved detection of rejection with the endomyocardial biopsy [9], and adoption of strict programs of surveillance for infection with the attending early and aggressive institution of therapy [4, 10, 11]. Infection and rejection continue to be the most common causes of death [1, 5, 12].

An early report on the results of cyclosporine-based immunosuppression for cardiac transplantation compared the incidence of death from infection prior to and after the use of cyclosporine. The conclusion was that infection remains the leading cause of death before the use of cyclosporine (89/167) and with its use (8/20), but that overall, the incidence of death from infection is significantly less frequent with its use [5].

Because no study has demonstrated the value of protective isolation in the prevention of infection after cardiac transplantation, we decided to alter the isolation protocols to compare the frequency and types of infection as well as the outcome in a group of recipients of cardiac allografts who were strictly isolated versus a comparable group of patients who were not. This report is a randomized study of recipients of cardiac allografts, and is designed to study the difference between protective isolation and no isolation as to the frequency of infection, the mortality related to infection, and the types of pathogens. It is a study of the relationship between the morbidity before transplantation and the development of infection after heart transplantation. Last, it addresses the difference between the protocol of immunosuppression and the occurrence of infection.

Material and Methods

Patients were admitted after cardiac transplantation to the surgical intensive care unit (ICU), a 16-bed, multidisciplinary unit with four private rooms and 12 beds in an open ward. Each of the private rooms is enclosed by walls and equipped with a sink. The 12 open beds have no physical dividers, and the entire area is serviced by four sinks. Cardiac recipients share the unit with recipients of liver transplants and patients who are on the trauma, neurosurgical, and general surgical services, many of whom have infection of the incision or pulmonary system.

Patients were randomized to protective isolation (PI) or no isolation (NI) before arrival in the surgical ICU. Those in protective isolation were placed in a private room in the surgical ICU. All persons who entered the room were required to don a hat, mask, gloves, and gown and to follow strict procedures for handwashing. Those randomized to no isolation were placed in the open unit. These patients received no special precautions for isolation, and only routine practices for handwashing were followed. When a patient was transferred from the surgical ICU, he or she was housed in a private room when possible, generally by the fourth postoperative day. Masks and

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handwashing were required for all persons who entered the room.

Categories of the severity of illness were identified and were used to analyze the comparability of the two groups (PI and NI). These categories were outpatient, inpatient, inpatient on inotropic support, and inpatient supported with an intraaortic balloon. Infections were categorized as to site, organism, treatment, and outcome. Patients were followed for the first 30 days after transplantation or to the end of hospitalization, whichever was longer. Morbidity and mortality were statistically analyzed on the basis of the first 30 postoperative days. At the end of the study, the records were reviewed to assure accuracy. Demographic and summary data were analyzed with descriptive statistics.

Results

Patient Characteristics

Sixty patients were studied between April and November 1987. Thirty were randomized to PI and 30 to NI by means of a table of random numbers. Age ranged from 16 to 64 years (mean age, 49.2 years). The mean age of the PI patients was 50.1 years and that of the NI group, 48.3 years. The cause of cardiac disease for the majority of patients was ischemic (58%) or idiopathic cardiomyopathy (33%). Two patients had a viral cardiomyopathy and 1 each, a congenital, valvular, postpartum, and amyloid cardiomyopathy. There was a comparable distribution of causes within the two groups (Table 1).

All patients were immunosuppressed with corticosteroids, azathioprine, and cyclosporine. In addition, each patient received either rabbit antithymocyte globulin intramuscularly for five days or murine monoclonal antibody OKT3 intravenously for 14 days unless serious complications arose that required premature termination. Assignment of patients was determined by a concomitant prospective trial that was designed to compare the efficacy of these two agents. Thirty-four patients (57%) received OKT3, and 26 (43%) received rabbit antithymocyte globulin. There was no difference in age, diagnosis, immunosuppression, morbidity before operation, days in the ICU and hospital, or outcome between the two groups (see Table 1).

Seventeen patients (28%) awaited transplantation as outpatients, 30% in the PI group and 27% in the NI group. Forty-three patients (72%) were inpatients before transplantation, 25 (58%) of whom were on inotropic medications and 8 (19%) of whom were supported by intraaortic balloon pumps. The preoperative morbidity was comparable between the groups (see Table 1). The median length of stay in the ICU was four days for the PI patients and 4.5 days for the NI patients, and the median stay in the hospital was 35 days for the PI patients and 33 days for the NI patients. There was no difference between the groups for these variables.

Mortality

Fifty-two patients (87%) were discharged from the hospital (see Table 1). Of the 8 patients who died, 4 died of infection (2 from each group) and 4 died of primary cardiac-related causes (graft failure or rejection) (3 in the PI group and 1 in the NI group).

Table 1. Summary of Patient and Hospital Data[a]

Description	PI Group (n = 30)	NI Group (n = 30)
Underlying cardiac disease		
Ischemic	18 (60)	17 (57)
Idiopathic	11 (37)	8 (26)
Viral	0 (0)	2 (7)
Other	1 (3)	3 (10)
Immunosuppression protocol		
RATG	12 (40)	14 (47)
OKT3	18 (60)	16 (53)
Pretransplantation morbidity		
Outpatient	9 (30)	8 (27)
Inpatient alone	5 (17)	5 (17)
Inpatient + drips	12 (40)	13 (43)
Inpatient + IABP	4 (13)	4 (13)
Postoperative ICU stay (days)	4	4.5
Total hospital stay (days)	35	33
Outcome		
Discharged	25 (83)	27 (90)
Died, infection	2 (7)	2 (7)
Died, other	3 (10)	1 (3)

[a] Numbers in parentheses are percentages.

IABP = intraaortic balloon pump; ICU = intensive care unit; NI = no isolation; PI = protective isolation; RATG = rabbit antithymocyte globulin.

The 4 patients who died of infection were predisposed because of multiple operations (Table 2). One patient (patient 16) required reopening of the incision in the ICU because of a cardiac arrest, 1 (patient 11) was reexplored for hemorrhage, 1 (patient 14) underwent resection of a pulmonary abscess early after transplantation, and another (patient 51) underwent a second cardiac transplantation, as the first graft failed because of the development of advanced atherosclerosis.

The infectious complications in these 4 patients are characterized by failure of multiple organs (Table 3). These patients experienced nine episodes of infection, primarily single bacterial and mixed bacterial infections. These infections were associated with progressive pulmonary and hepatic failure, and ultimately renal failure that required hemodialysis.

Analysis of Infection

Infections developed in 31 (52%) of the 60 patients. Eighteen patients had one infection, 7 had two, and 6 had three. There was a total of 51 episodes. An equal percentage in each group had at least one infection. Seventeen of the 30 patients in the PI group and 14 of the 30 NI group contracted an infection (Table 4). Seven in the PI group and 6 in the NI group had more than one infection.

The distribution of pathogens in each group is comparable except for a significantly increased incidence of fungal infections in the NI patients ($p = 0.052$) (Table 5).

Table 2. Data for 4 Patients Who Died of Infection

Patient No.	Age (yr)	Sex	Isolation Protocol	OKT3 or RATG	Pretransplantation Morbidity	Diagnosis	Complications
11	24	F	NI	OKT3	Outpatient	Congenital	Reoperation for bleeding, day 1; hemodialysis, day 6; cardiac arrest, day 9; elevated bilirubin, day 10; died, day 23.
14	16	M	NI	OKT3	Mechanical support	Idiopathic	Persistent fever, day 5–30, with atypical lymphocytosis, day 8; elevated bilirubin, day 12; left lower lobectomy for lung abscess, day 16; hemodialysis, day 26; died, day 33.
16	47	M	PI	RATG	Inpatient alone	Ischemic	Cardiac arrest, day 1, with open-chest cardiac massage; Jarvik-7 implantation, day 1, for cardiac failure; retransplantation, day 8; hemodialysis, day 12; died, day 20.
51	43	M	PI	RATG	Mechanical support	Ischemic	Allograft CABG; preoperatively on IABP and inotropic agents for 6 days; persistent cardiogenic shock; multiple-organ failure; hemodialysis, day 7; died, day 10.

CABG = coronary artery bypass grafting; IABP = intraaortic balloon pump; NI = no isolation; PI = protective isolation; RATG = rabbit antithymocyte globulin.

Of the 5 fungal infections in the NI group, 4 were oral with *Candida albicans* and 1 was a urinary tract infection with the same fungus; there were no fungal infections with PI. Altogether, patients with PI had 27 infections and patients with NI, 24. Overall, 41% of the infections were bacterial, 43% were viral, 10% were fungal, and 6% were protozoal.

The most common site of infection was the oral cavity (19 episodes or 37%, nine with PI and ten with NI (Table 6). Most episodes were due to herpes simplex. The next most common sites were the urinary tract (eight episodes or 16%) and lung (seven episodes or 14%). The urinary tract infections were divided equally between the two groups, and pneumonia developed in 3 PI patients and 4 NI patients. Four soft tissue infections occurred with PI: one localized staphylococcal abscess at the site of a chest tube, one case of phlebitis from an intravenous catheter, and two cases of cellulitis without evident cause. Three septic episodes with positive blood cultures occurred with PI and two with NI. A small but equal number of

Table 3. Infectious Complications in Patients Who Died of Infection

Patient No.	Source of Infection	Organism	Onset (week postop)
11	Bacteremia	*Enterobacter cloacae*	2
	Pneumonia	*Pseudomonas aeruginosa*	2
	Wound infection	*Pseudomonas aeruginosa*	2
	Urinary tract	*Candida stellatoidea*	2
14	Pneumonia	*Acinetobacter anitratus, Staphylococcus aureus*	2
	Lung abscess	Diphtheroids	3
	Disseminated[a]	Epstein-Barr virus	
16	Pneumonia with bacteremia	*Klebsiella, Haemophilus influenzae, Serratia marcescens*	2
	Bacteremia	*Serratia marcescens,* Enterococcus	2
51	Pneumonia	*Pseudomonas aeruginosa*	1

[a] This was lymphoproliferative disease with primary infection, and was diagnosed at autopsy.

Table 4. Incidence of Infections and Number of Infectious Episodes for Each Isolation Group[a]

Isolation Protocol	Incidence of Infection[b]	Total No. of Infectious Episodes[c]
Protective isolation (n = 30)	17 (57)	27
No isolation (n = 30)	14 (47)	24

[a] Numbers in parentheses are percentages. [b] Significance: χ^2 (1) = 0.27 (χ^2 with Yates' correction), $p = 0.6$ (not significant). [c] Significance: χ^2 (1) = 0.52 (χ^2 with Yates' correction), $p > 0.10$ (not significant).

Table 5. Distribution of Pathogens by Isolation Protocol[a]

Type of Pathogen	Infectious Episodes: Protective Isolation	Infectious Episodes: No Isolation
Viral	13 (48)	9 (38)
Bacterial	12 (44)	9 (38)
Fungal	0 (0)[b]	5 (21)[b]
Protozoal	2 (7)	1 (4)

[a] Numbers in parentheses are percentages. [b] Significance: $p = 0.052$ by Fisher's exact test (two-tailed).

Table 7. Summary of Infection Data for Each Immunosuppression Protocol Group

Variable	Immunosuppression Protocol: RATG (n = 26)	Immunosuppression Protocol: OKT3 (n = 34)
Patients with infection	11 (42%)[a]	21 (62%)[a]
Total infectious episodes	22 (0.85/patient)	29 (0.85/patient)
Infection-related deaths	2	2

[a] Significance: $\chi^2 = 1.52$, $p > 0.05$.
RATG = rabbit antithymocyte globulin.

infections of the upper respiratory tract developed with PI and NI. One case of mediastinitis and one case of a lung abscess developed only in the group with NI. The patient in whom the lung abscess developed had a pulmonary infarction preoperatively that predisposed him to the formation of the lung abscess, and he subsequently died of disseminated lymphoproliferative disease.

As there were two protocols of immunosuppression, the proportion of patients in each protocol in whom one or more infections developed was analyzed (Table 7). One or more infections developed in 62% of those who received OKT3 and 42% of those who received rabbit antithymocyte globulin, which was not significantly different ($\chi^2 = 1.52$, $p > 0.05$). The total number of infectious episodes per patient in each group (0.85) was equal.

The magnitude of illness before transplantation did not predispose patients to a greater chance of infection, as an equal proportion of patients in each category had infections (Table 8), and the 4 infection-related deaths were fairly evenly distributed throughout the categories.

Comment

Before the use of cyclosporine, recipients of cardiac transplants were maintained on azathioprine, corticosteroids, and antithymocyte globulin. Several studies [13, 14] demonstrated that infection limited survival with this regimen of immunosuppression. Investigators [10, 15–17] from a number of transplant centers have examined infectious complications in recipients of cardiac transplants since the introduction of cyclosporine. Baumgartner [15] stated that with the addition of cyclosporine, "the number and severity of infections has decreased in comparison with patients who were treated with a conventional prednisone-azathioprine regimen. However, the same opportunistic organisms will remain a threat to the cardiac transplant recipient."

Complications related to infection accounted for 41% of all deaths among patients who received heart or heart-lung transplants between 1967 and 1981 [1]. Bacteria remain the most common pathogen, but fungal, viral, and protozoal organisms are responsible for a substantial portion of the infections in recipients of cardiac transplants. All these organisms contribute to the mortality that is a result of infection. In our study, viruses (22 episodes) were as common as bacterial infections (21 episodes), but significantly more common than fungal (5 episodes) or protozoal infections (3 episodes).

Early protocols for protective and reverse isolation protocols [18, 19] were based largely on concerns about the morbidity and mortality due to infection. Several studies evaluated the efficacy of protective isolation in granulocytopenic patients. Buckner and associates [20] devised a prospective randomized study of isolation with laminar air flow and decontamination for patients with aplastic anemia and leukemia who had undergone bone marrow transplantation. Patients treated with decontamination and given a room with laminar air flow had significantly fewer episodes of septicemia and major local

Table 6. Sites of Infection According to Isolation Protocol[a]

Site of Infection	Protective Isolation	No Isolation
Oral cavity	9 (33)	10 (42)
Urinary tract	4 (15)	4 (17)
Lung (pneumonia)	3 (11)	4 (17)
Blood	3 (11)	2 (8)
Soft tissue	4 (15)	0 (0)
Upper respiratory tract	2 (7)	1 (4)
Bowel	2 (7)	1 (4)
Lung (abscess)	0 (0)	1 (4)
Mediastinum	0 (0)	1 (4)
Total	27	24

[a] Numbers in parentheses are percentages.

Table 8. Frequency of Infection and Infection-Related Mortality for Each Pretransplantation Morbidity Class[a]

Pretransplantation Morbidity	Patients With Infection(s)	Infection-Related Deaths
Outpatient (n = 17)	10 (59)	1
Inpatient alone (n = 10)	5 (50)	0
Inpatient + inotropic agents (n = 25)	13 (52)	2
Inpatient + IABP (n = 8)	4 (50)	1

[a] Numbers in parentheses are percentages.
IABP = intraaortic balloon pump.

infections than patients in the control group. In both groups, however, infections were noted to be "related to the severity of granulocytopenia, with most infections occurring at granulocyte levels of $<100/\text{mm}^3$." Nauseet and Maki [21] conducted a prospective study of protective isolation in granulocytopenic patients who had leukemia, and compared the rates of infection in two groups. No difference was seen in the incidence of infection between the patients who were treated with protective isolation and the controls.

Many protocols for protective isolation include a private room. In a unique study of colonization and infection, Preston and co-workers [22] took advantage of the conversion of their ICU from an open ward to individual rooms. The institution of individual rooms did not reduce the nosocomial infections, nor did the redesign alter the incidence of colonization and infection in the ICU.

The early reports of cardiac transplantation alluded to the use of reverse or protective isolation. Barnard [18] described the use of a "sterilized plastic tent" for transport from the operating room, but no mention was made of protocols for protective isolation during the postoperative course. To date, little objective evidence exists to support the need for protective isolation in patients after cardiac transplantation. Three relatively recent reports [23–25] indicated a limited role for protective isolation in terms of the incidence of infection after cardiac transplantation. Protocols of protective isolation can be time-consuming for the nurses, difficult to monitor for compliance, costly to implement, and detrimental to the patient's emotional well-being [24–26]. As more demands are placed on programs of cardiac transplantation to expand services and more transplantations are done outside of the specialty centers, the rationale for protected environments needs to be addressed. This scrutiny maximizes the allocation of both human and material resources while the effort is made to safeguard the immunosuppressed patient from infection.

Current centers of cardiac transplantation have chosen to base their protocols for protective isolation on those of the initial centers of transplantation, which seemed a safe and efficacious practice. The techniques of isolation were based on tradition with little supporting scientific evidence. This has contributed to discrepancies in procedures among and within centers of transplantation. At the University of Pittsburgh, recipients of liver, pancreas, and kidney allografts receive no special precautions for protective isolation, whereas recipients of cardiac transplants have been treated with a modified form of protective isolation for at least 3 weeks postoperatively. This consisted of a private room and required persons entering the room to wear a mask and wash their hands.

Recipients of a cardiac transplant infrequently become so severely granulocytopenic with the conventional regimens of immunosuppression that a totally protected environment is required. The use of simple protective isolation would seem questionable [26]. Nonetheless, most cardiac centers have adopted some procedures for protective isolation. Some studies [23, 25, 27] have examined in a retrospective fashion the impact of isolation on the incidence of infection after cardiac transplantation and have reported no advantage. In a report on the sites of infection in 44 recipients of cardiac transplants who were treated with protective isolation, Hess [24] concluded that the reduction of the isolation restrictions lowered the costs of the patient's stay in the hospital without increasing the risk of infection.

We have demonstrated that isolation did not protect recipients of cardiac allografts. Whether a patient was kept in strict isolation or placed in an open ward with a variety of surgical patients did not significantly affect the type, location, or frequency of infections. The 2 deaths due to infection in each of the groups were caused by gram-negative pathogens with a predominance of pneumonia. One patient in the group with protective isolation died of bacterial pneumonia and bacteremia after transplantation preceded by seven days of support on a Jarvik-7 artificial heart. We [28] have shown that the risk of infection is higher in patients supported with the artificial heart as a bridge to transplantation.

There was an increased incidence of minor fungal infections in the patients not in protective isolation. No breach in care after transplantation was detected on review of the records, but again, none of the infections progressed to a systemic infection. Infections in soft tissues were absent in the patients not in isolation, whereas 15% of the isolated patients contracted a cellulitis or phlebitis. No differences between the two groups could be found in length of ICU stay, use of invasive monitoring, or placement of drainage tubes.

Oral infections with herpes were not more frequent in the patients not in isolation. This supports the argument that many of the infections seen after transplantation are reactivations of endogenous infections, which cannot be controlled by protective isolation. Many of the pathogens against which protective isolation is aimed require more than casual contact to be spread to a recipient.

The severity of illness before transplantation did not affect the frequency of infection after transplantation. Many of the infections after transplantation arise from endogenous, opportunistic organisms that are not affected by either the severity of illness before transplantation or the protocols for isolation of the nongranulocytopenic recipient of a cardiac allograft. Perhaps the absolute magnitude of immunosuppression and the need for more than one thoracic operation are of greater importance in the determination of the morbidity and mortality due to infection. Better means to monitor the degree of immunosuppression in recipients may be of benefit in minimizing the morbidity and mortality caused by infections.

As a result of our findings and the extra expense of strict isolation, as well as the limitations placed on contact with visitors and personnel from the hospital, we have stopped the routine use of protective isolation for recipients of cardiac transplants.

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DISCUSSION

DR WILLIAM A. BAUMGARTNER (Baltimore, MD): Clinical heart transplantation has now been practiced for more than 20 years. Infection was and remains the primary cause of death in transplant recipients, both in the early postoperative period and in the long-term follow-up. In an attempt to reduce this incidence, stringent isolation protection was initially employed during the decade of the 1970s. Although the introduction of cyclosporine has reduced the number of deaths associated with infection, the incidence has remained approximately the same. As programs witnessed the declining incidence of lethal infection, isolation precautions were progressively reduced. However, to my knowledge, no randomized trial examining the efficacy of isolation procedures has been performed until now.

As in previous transplantation studies, the authors have addressed a traditionally accepted practice in a scientific manner utilizing a prospective randomized trial. Their series of 60 heart transplant recipients involved randomization to two types of isolation procedures, as described by Dr Walsh. The traditional one of reverse isolation, emphasizing a private room, hat, mask, sterile gown, and handwashing, was compared with no special isolation except for standard handwashing.

There were 8 hospital deaths, a 13% perioperative mortality, and of those deaths, 4 were due to infection, 2 in each of the isolation groups. The authors were unable to show any significant correlation between the type of protective isolation and the incidence of infection, nor was there a difference in infection based on pretransplantation morbidity. Randomization provides credibility to the study, although I think the short duration of randomization, that is, four days, weakens it somewhat. My first question for Dr Walsh is whether, with the small numbers of patients studied, four days of randomization is adequate to show a real difference.

A review of our own transplant series of 94 patients showed there were 4 hospital deaths. Two of the 4 patients died of multiorgan failure and infection. In retrospect, both patients were marginal candidates for transplantation. Because recipient selection was important in the outcome for 2 of our 4 patients who died, I would appreciate it, Dr Walsh, if you would comment further regarding the pretransplantation morbidity in your 4 patients who died of infection. In reading the manuscript, I noted that 2 of these patients required hemodialysis on days 6 and 7, 1 patient required left lower lobectomy on day 16 because of a preoperative pulmonary infarction, and 1 patient received a Jarvik-7 heart, which, as your group has shown in the past, is frequently associated with mediastinitis and death from infection. Have you assessed recipient selection criteria in view of these perioperative deaths?

Our initial isolation protocol was complete reverse isolation, which was in place for the first 4 years of our program. Starting in June 1987, we replaced that with a more simplified practice when we moved into a new intensive care unit. At present, we place the patient in a private room and maintain face mask and good handwashing as the only protective precautions.

We also have not seen an increase in infection rates with this protocol. Our findings support the results obtained in this study. However, I believe that if a hospital has a private room in the ICU, it should be utilized for the transplant patient. It does remind personnel of the need to exercise good aseptic technique between patients. This type of reduced isolation protocol is advantageous to the patient and the family, and helps minimize the cost of the transplant procedure.

My final question is whether the present protocol at Pittsburgh continues to make use of private rooms with face mask and handwashing when the patient is discharged from the ICU. We agree with the authors that at present, the evidence supports the theory that strict isolation procedures are no longer needed for the heart transplant recipient.

DR WALSH: Thank you very much, Dr Baumgartner, for your comments. They are very appropriate.

The randomization process was based on some practical reasons as well as some advice from our infectious disease colleague, which is twofold. First, his major concern is the immediate perioperative period, and especially the first several days after transplantation, as far as acquired infections are concerned, as opposed to reexacerbation of endogenous infections. In this study, as in most that review infections in cardiac transplant recipients, a majority of infections are due to reactivated endogenous infections, oral herpes, or similar causes. Therefore, the days that were considered to be most important for acquiring infections were the immediate perioperative days in the ICU.

The second aspect is simply a practical application. Prior to the building of our new unit, we had a very crowded situation on the regular cardiac care floor. It was difficult to continue the isolation precautions for each patient. Consequently, they all received routine care, which, as you mentioned, consisted of face masks and washing of hands. The present protocol does not include these precautions. When the patients are brought up to the floor, they are in a private room, and face masks are not worn. Handwashing is recommended for all visitors, but there is no strict monitoring of this.

As for the selectivity of our recipient selection process, in the past, the University of Pittsburgh heart transplant surgeons have not been selective because of the large referral base and large number of donors available. As the donor pool becomes more restricted, especially for large referral centers, it may become clearer whether any particular subgroup of patients can benefit from protective isolation.

Right Atrial Approach for Surgical Correction of Tetralogy of Fallot

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Total correction of tetralogy of Fallot was performed without a ventriculotomy in 39 patients aged 8 months to 39 years (mean age, 9.1 years) between May 1984 and July 1988. A transatrial approach was used to resect the obstructed infundibulum and to close the ventricular septal defect. In 14 patients, the pulmonary annulus was not enlarged (group 1). Twenty-five patients required a transannular patch (group 2), placed by extending the pulmonary artery incision 1 cm into the right ventricular infundibulum. Eleven patients had repair of pulmonary artery branch stenosis, and associated intracardiac anomalies were simultaneously corrected in 10 patients. After repair, the right ventricular to left ventricular systolic pressure ratios ranged from 0.36 to 0.59 (mean ratio, 0.45) in group 1 and 0.33 to 0.70 (mean ratio, 0.51) in group 2. There were no hospital or late deaths in group 1. Two patients in group 2 with a small left ventricle died shortly after operation. The 37 survivors were followed for 2 to 51 months. Postoperative catheterization in 7 patients detected no residual ventricular septal defects, mild pulmonary regurgitation in 2 patients (group 2), and right ventricular to left ventricular pressure ratios ranging from 0.25 to 0.42 (mean ratio, 0.34). Only 1 patient with a previous total repair by ventriculotomy is symptomatic and requires antiarrhythmic agents and diuretics. The other 36 patients are asymptomatic. In conclusion, tetralogy of Fallot can be safely repaired at any age without a ventriculotomy. The results indicate a minimal incidence of postoperative arrhythmias and pulmonary regurgitation, as well as improved right ventricular function.

(Ann Thorac Surg 1989;47:546–52)

Surgical correction of tetralogy of Fallot through a "classic" right ventriculotomy has been performed since 1955 [1]. The results have improved steadily with modern surgical techniques, myocardial protection, and refined postoperative care. It has been demonstrated that very satisfactory hemodynamic results can usually be obtained with a conventional transventricular approach [2, 3]. The surgical risk for patients more than 1 year of age is currently less than 5% in most centers [4]; it is less than 2% for patients older than 2 years [4]. Early repair during infancy can also be accomplished with very low mortality rates [5–8].

However, late sudden deaths secondary to ventricular arrhythmias [9, 10] and chronic right ventricular dysfunction [11–13] are undesirable events caused by a right ventriculotomy incision. Therefore, it has been suggested that these long-term sequelae might be avoided by correcting this anomaly through a right atriotomy. Hudspeth and colleagues [14] described this technique in 1963. Since then, several authors [15–18] have shown that the obstructed infundibulum can be relieved very adequately with a minimal ventriculotomy or no ventriculotomy at all.

The purpose of this study is to present our experience with the transatrial approach, to outline some technical considerations, and to discuss its potential advantages.

Material and Methods

Patient Population

Between May 1984 and July 1988, a total of 39 patients underwent surgical correction of tetralogy of Fallot by the transatrial approach. There were 23 female and 16 male patients ranging in age from 8 months to 39 years (mean age, 9.1 years), including 5 infants less than 1 year of age and eight adults (older than 18 years). Weight ranged from 5.9 to 76 kg.

All patients were symptomatic before operation (Table 1). Eight who had hypoxic spells were prescribed propranolol hydrochloride to delay surgical intervention. Another 12 patients had undergone a previous palliative operation: five polytetrafluoroethylene, five Blalock-Taussig, and two Waterston shunts. In addition, 3 patients who had had a previous "correction" utilizing a right ventriculotomy required reoperation because of severe residual right ventricular obstruction as well as a ventricular septal defect and tricuspid regurgitation.

Preoperative echocardiography was performed in every patient, and cardiac catheterization was performed in all but 1 child who was extremely hypoxic and acidotic because the polytetrafluoroethylene shunt, which had functioned well for several years, occluded suddenly. In comatose condition, she underwent an emergency operation for total repair, and recovered completely and uneventfully. A representative preoperative right ventricular angiocardiogram is shown in Figure 1.

Associated intracardiac anomalies were detected in 10 patients (Table 2). Eleven patients also had a major

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Table 1. Preoperative New York Heart Association Functional Class

Class	Age (yr) 0–1	1–18	>18	Total
I	0	0	0	0
II	0	17	2	19
III	5	8	6	19
IV	0	1	0	1
Total	5	26	8	39

stenosis in one or both pulmonary arteries, four of which were directly related to previous palliative procedures (two Waterston and two polytetrafluoroethylene shunts). Two patients (aged 12 and 24 months) had a left ventricular end-diastolic volume of 60% and 70% of normal, respectively, by echocardiographic and angiographic criteria. The size of the pulmonary annulus was adequate in 14 patients (group 1), but was considered too small in 25 patients who required transannular patching (group 2).

Surgical Technique

A median sternotomy incision and standard cardiopulmonary bypass with moderate systemic hypothermia at 28°C were used in all patients. Cold potassium crystalloid cardioplegia and topical hypothermia were used for myocardial protection. Deep hypothermia with circulatory arrest was not used in this series. Systemic–pulmonary artery shunts were dissected before cardiopulmonary bypass was instituted, and were ligated immediately after perfusion started. A vent was placed in the left atrium through the right superior pulmonary vein to decompress the heart. The aortic cross-clamp time ranged from 31 to 82 minutes (mean time, 45 minutes); it was longer than 60 minutes in only 3 patients, 2 with a previous Waterston shunt and 1 child with coexisting complete atrioventricular canal.

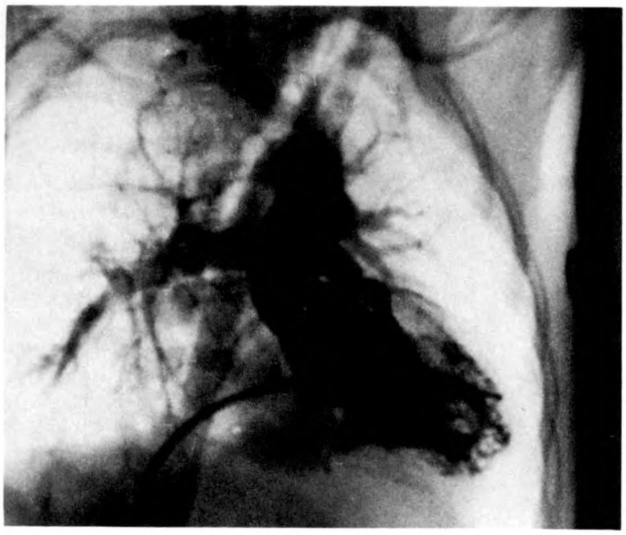

Fig 1. Preoperative right ventricular angiocardiogram of a 9-month-old infant with tetralogy of Fallot who had repair using a right atriotomy.

Table 2. Associated Anomalies[a]

Anomaly	No. of Patients
Patent ductus arteriosus	2
Atrial septal defect	2
Atrioventricular canal defect	1
Multiple ventricular septal defects	1
Pulmonary valve agenesis	2
Aortic valve prolapse	1
Anomalous left coronary artery	1
Unilateral pulmonary artery branch stenosis	9
Bilateral pulmonary artery branch stenosis	2
Tricuspid regurgitation (after repair)	3

[a] A total of 10 patients had associated anomalies, sometimes more than one per patient.

Intracardiac repair consisted of a right atriotomy and initial exploration through the tricuspid valve. In the 14 patients constituting group 1, there was no need to enlarge the pulmonary annulus. After transatrial infundibular resection was done, a pulmonary commissurotomy was possible through the right atrium in 4 patients. The other 10 patients required a pulmonary arteriotomy to incise the fused commissures, and 4 of them needed a supravalvular pericardial patch (1 with a previous Waterston shunt, 2 with stenosis at the pulmonary artery bifurcation, and 1 infant, in whom it was required to avoid narrowing of the main pulmonary artery after closure).

In the 25 patients in group 2 (64.1% of this series), it was necessary to extend the pulmonary arteriotomy across the pulmonary annulus to enlarge it. An acceptable transannular patch could be placed by extending the incision only 8 to 10 mm into the right ventricular infundibulum.

The pulmonary valve leaflets were completely resected if they were thickened. Otherwise, the fused commissures were simply divided. In this group of patients, it was easier to start the infundibular resection from the "transpulmonary" approach by incising the parietal and septal extensions of the infundibular septum (Fig 2).

After incision of the infundibular septum, attention is directed to the right atriotomy, and the tricuspid valve is retracted. The infundibular septum, which is anteriorly displaced in this anomaly, can be easily identified toward the left of the aortic valve because the heart is rotated 90 degrees to the patient's left. The parietal extension of the infundibular septum is now visible anteriorly and can be completely excised using the transatrial approach. The septal band is on the left and located inferiorly in relation to the right ventricular outflow tract. It is also resected through this approach (Fig 3).

During this part of the procedure, care must be taken to avoid injury to the papillary muscles and chordal attachments of the tricuspid valve. Based on data reported by Rowlatt and colleagues [19], the size of the right ventric-

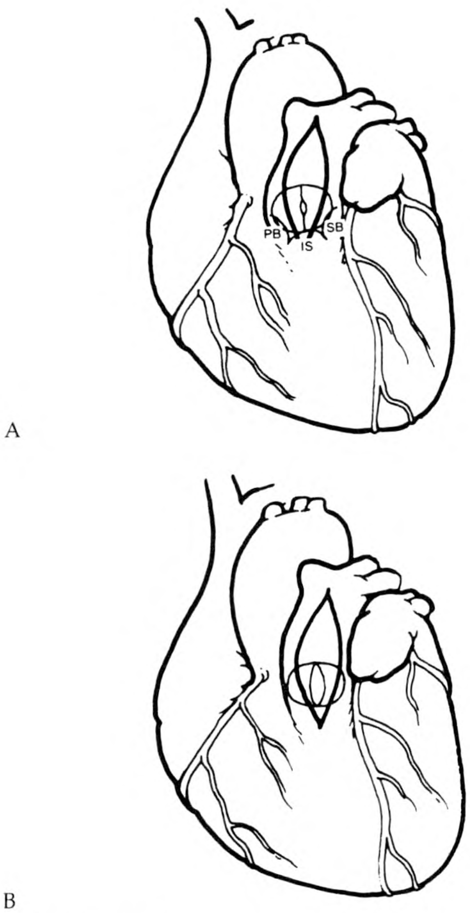

Fig 2. Pulmonary arteriotomy and its relationship to the infundibular septum (IS), *the parietal band* (PB), *and the septal band* (SB) *(A) before and (B) after infundibular resection.*

ular outflow tract and pulmonary annulus are determined with Hegar's dilators to assure adequate relief of obstruction.

In general, infants require transannular patching and minimal resection of the infundibular septum and the obstructive bands, which are less hypertrophied at this age. A pericardial patch is used in all patients, when indicated, to enlarge the pulmonary annulus and areas of stenosis in the pulmonary artery branches (Table 3). During rewarming, the ventricular septal defect is closed with a Dacron patch. This also is done through the right atriotomy.

In our series, associated defects were present in 10 patients (see Table 2) and were repaired concomitantly during operation. The atrial septal defects, the atrioventricular canal defect, and the multiple muscular ventricular septal defects were also repaired without a ventriculotomy using the same atrial approach. The patients with pulmonary valve agenesis had a bioprosthetic valve implanted at the level of the annulus (which was enlarged), and a large wedge of the aneurysmal pulmonary artery was excised. Nothing additional was done to the patient with an anomalous left anterior descending coronary artery originating from the right coronary artery. This approach is ideal in such patients because a ventriculotomy might injure the anomalous coronary vessel, and the use of a conduit is avoided.

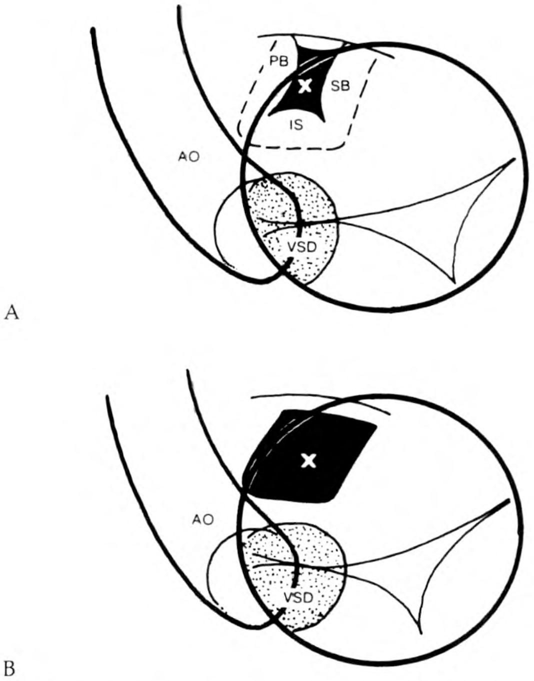

Fig 3. Structures visualized across the tricuspid valve: ventricular septal defect (VSD), *aorta* (AO), *infundibular septum* (IS), *parietal band* (PB), *and septal band* (SB). X *represents the size of the infundibulum (A) before and (B) after transatrial resection of the obstruction.*

Pressures were measured in the operating room before the sternum was closed. The right ventricular to left ventricular systolic pressure ratios ranged from 0.36 to 0.59 (mean ratio, 0.45) in patients without annular enlargement (group 1) and from 0.33 to 0.70 (mean ratio, 0.51) in those with a transannular patch (group 2).

Results

Transatrial resection of the obstructed infundibulum is very effective, as demonstrated by the right ventricular to left ventricular pressure ratios after the procedure was completed.

The overall hospital mortality in this series was 5.1%. There were no deaths in group 1. However, 2 patients with a transannular patch died shortly after surgical repair. Both of them had been medicated with propranolol for several months before operation, and both had a small left ventricular dimension (less than 75% of normal)

Table 3. Use of Transannular Patch by Age Group

	Age (yr)			
Group	0–1	1–18	>18	Total
1 (Without transannular patch)	2	8	4	14
2 (With transannular patch)	3	18	4	25
Total	5	26	8	39

by echocardiographic and angiographic studies. One was a 2-year-old child who died in a low-output state 12 hours postoperatively, and the other was a 1-year-old infant who was in stable condition until the right atrial and left atrial monitoring lines were removed 48 hours after operation. Cardiac tamponade developed, and the patient went into cardiac arrest and could not be resuscitated. There were no late deaths in either group.

Nonfatal postoperative complications included postpericardiotomy syndrome, which improved with aspirin and diuretics (4 patients), mediastinitis (1 patient), superficial wound infection (1 patient), and seizures secondary to hypocalcemia, without neurological sequelae (1 infant).

Transient atrioventricular dissociation was noted in 2 patients, but normal sinus rhythm resumed spontaneously a few days later. A pattern of right bundle-branch block was evident on the electrocardiogram (ECG) of all 39 patients. One adult had a permanent pacemaker before the transatrial repair was done. It had been implanted in 1976 when complete heart block was produced at the time of transventricular "correction."

Nine patients (23%) required inotropic support during the initial 24 to 48 hours after operation. Six of 8 patients who had received propranolol preoperatively required dopamine hydrochloride infusion postoperatively, whereas only 2 of 12 with a previous shunt needed inotropic drugs. Also, 1 adult who had undergone a prior transventricular repair and was in congestive heart failure required dopamine and diuretics. It is noteworthy that none of the patients with a previous shunt, not even the child with acute occlusion of the shunt, had complications after operation.

Follow-up ranged from 2 to 51 months (mean duration, 23.7 months). The only symptomatic patient was the adult who had undergone a previous repair using a right ventriculotomy and had also had a permanent pacemaker implanted at that time. This patient was in severe congestive heart failure before reoperation, which was indicated because of residual right ventricular obstruction, a ventricular septal defect, and severe tricuspid regurgitation. After transatrial repair of all these defects, he is now in New York Heart Association functional class II, and still requires diuretics and antiarrhythmic agents. This was the first patient operated on in our series. It was very helpful to avoid a repeat ventriculotomy because the right ventricular function of this patient was seriously impaired. The remaining 36 patients are asymptomatic and are in New York Heart Association functional class I. Only 1 of them, an adult who had a previous transventricular repair in 1971, is taking antiarrhythmic medications.

A 1/6 or a 2/6 midsystolic ejection murmur is present in most patients, and only 12 have a soft diastolic murmur consistent with mild pulmonary regurgitation. In 18 patients, the chest roentgenogram shows mild to moderate cardiomegaly. However, the postoperative echocardiogram reveals normal contractility in every patient except 1 (with a previous ventriculotomy), and the right ventricular outflow tract is free from obstruction in all patients (Fig 4).

The patient with a permanent pacemaker also has ventricular extrasystoles on routine ECGs. The other 36 patients have a normal resting ECG without ventricular ectopy. Ambulatory 24-hour Holter monitoring was performed in 19 patients, and multiple premature ventricular beats were detected in the adult already mentioned who had a previous ventriculotomy in 1971. Therefore, the only 2 patients in this series with ventricular arrhythmias are adults who had undergone a previous "correction" using a ventriculotomy. Postoperative cardiac catheterization and electrophysiological studies revealed a normal right ventricular pressure in both, and the site of reentry was at the level of the old ventriculotomy scar.

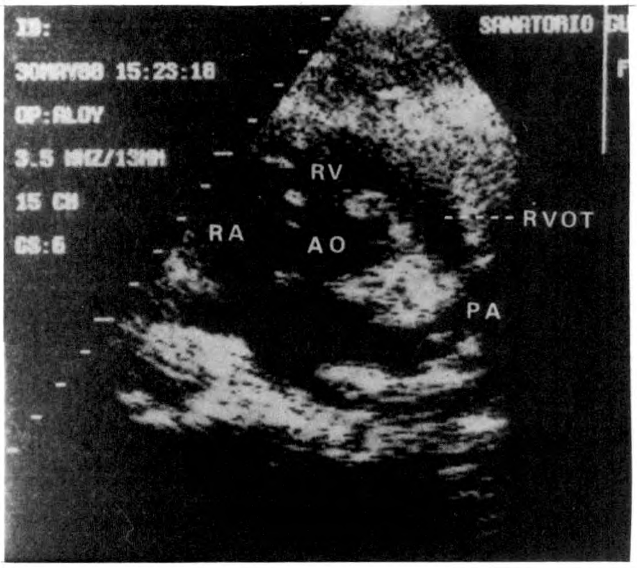

Fig 4. Postoperative echocardiogram of a 3-year-old patient after transatrial repair of tetralogy of Fallot. (AO = *aorta;* PA = *pulmonary artery;* RA = *right atrium;* RV = *right ventricle;* RVOT = *right ventricular outflow tract.*)

Of a previous group of 63 patients who underwent transventricular repair of tetralogy of Fallot between September 1980 and October 1984, and are not considered in this study, 24-hour Holter monitoring was done in 40. Multiple ventricular arrhythmias were detected in 8 of them, thus indicating that the classic approach is associated with a higher incidence of ventricular arrhythmias.

Postoperative cardiac catheterization was done in 5 other asymptomatic patients between 12 and 18 months after transatrial repair. There were no residual ventricular septal defects. Mild pulmonary regurgitation was detected in 2 patients with a transannular patch, and the right ventricular to left ventricular systolic pressure ratios ranged from 0.25 to 0.42 (mean ratio, 0.34). A normal configuration of the right ventricular outflow tract is shown in Figure 5.

Comment

Our present policy is to perform elective repair of tetralogy of Fallot in patients older than 2 years when the clinical condition is stable and cyanosis is mild, as Kirklin and colleagues recommend [20]. We also prefer to palliate with a polytetrafluoroethylene shunt all symptomatic infants younger than 6 months, although they represent a minority of the patients with tetralogy of Fallot [20].

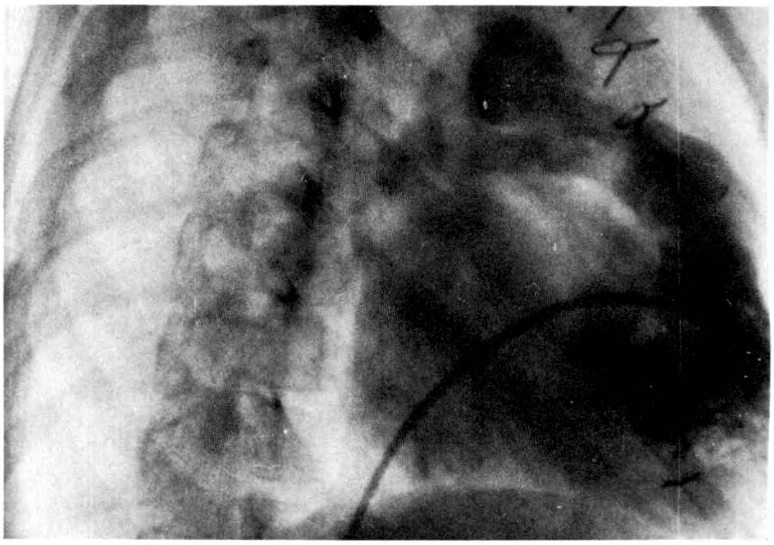

Fig 5. Postoperative right ventricular angiocardiogram of a 5-year-old child with tetralogy of Fallot obtained 18 months after repair by the right atrial approach.

Patients between 6 and 24 months of age who have hypoxic spells or increasing cyanosis with polycythemia are candidates for a corrective procedure if the anatomy is favorable [21, 22]. However, a two-stage repair with initial shunting is preferred in patients with severe hypoplasia of the pulmonary arteries [21, 22]. Earlier in our experience, symptomatic infants received propranolol as palliative treatment, as suggested by Garson and associates [23], to delay repair until the age of 2 years. We no longer use this method of palliation except for brief periods. Currently, symptomatic infants undergo surgical repair or palliation, depending on the anatomy.

It was reported by Nomoto and colleagues [24] and Hammon and associates [25] that a small left ventricular size is an incremental risk factor. In our series, the 2 deaths occurred in patients with a left ventricular end-diastolic volume less than 75% of normal. For this reason, we now also prefer a preliminary shunt in infants with a small left ventricular cavity, as Naito and co-workers [26] recommend.

Our results indicate that age less than 2 years, prolonged treatment with propranolol in patients with hypoxic spells, and the need for a transannular patch increase the risk of operation to some extent (Table 4).

Since May 1984, we have used a right atrial approach for intracardiac repair of tetralogy of Fallot in 39 patients in all age groups. The efficacy of this technique has been demonstrated by Edmunds and colleagues [15], Kawashima and associates [16], Pacifico and colleagues [17], McGrath and Gonzalez-Lavin [18], and others. We believe the transatrial approach offers several advantages. First, the long-term function of the right ventricle is preserved when a ventriculotomy is avoided, whereas an incision in the right ventricle reduces its contractility and causes necrosis of the adjacent myocardium [11, 12, 15].

Second, the risk of injuring a major ventricular branch of the right coronary artery or an anomalous left coronary artery is minimized with this technique, which is particularly useful in such cases [15].

Third, the ventriculotomy scar can be the site of origin of serious life-threatening ventricular arrhythmias [9, 10]. Therefore, the transatrial approach is advisable to reduce the risk of late sudden death. Further investigation is required before a definitive conclusion is made because ventricular arrhythmias can also be related to older age at operation, longer interval after operation, and right ventricular hypertension [10, 27, 28]. Nonetheless, major ventricular arrhythmias can occur late postoperatively after a transventricular repair, even with excellent hemodynamic results, because of a reentrant mechanism at the ventriculotomy scar [29, 30].

Fourth, the resultant pulmonary regurgitation after limited transannular patching is less severe than that which often occurs after transventricular repair [17].

In summary, tetralogy of Fallot can be safely repaired by a transatrial approach at any age, thereby avoiding a ventriculotomy. The objective is to reduce the incidence of chronic right ventricular dysfunction, the risk of late sudden death secondary to ventricular arrhythmias, and the severity of pulmonary regurgitation.

Table 4. Risk Factors[a]

Factor	Deaths/Patients[b]
Small left ventricle	2/2 (100)
Age (yr)	
<1	1/5 (20)
1–2	1/5 (20)
>2	0/29 (0)
Propranolol and hypoxic spells	2/8 (25)
With transannular patch	2/25 (8)
Without transannular patch	0/14 (0)
Pulmonary artery branch stenosis	1/11 (9)
No pulmonary artery branch stenosis	1/28 (4)
Associated cardiac anomalies	0/10 (0)
Previous operation	0/15 (0)

[a] Numbers in parentheses are percentages. [b] The overall mortality was 2 of 39 patients (5.1%).

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DISCUSSION

DR ALBERT D. PACIFICO (Birmingham, AL): I congratulate Dr Dietl and his associates on this fine presentation, and I am grateful for the privilege of reviewing the manuscript in advance.

In July 1981 on one surgical service at the University of Alabama in Birmingham, we began to repair classic tetralogy of Fallot through a transatrial-transpulmonary approach. In 109 consecutive patients operated on through June 1987, transatrial repair was accomplished in 98 patients, 90% of the group. The most common contraindication to transatrial repair was the presence of a hypoplastic and tubular infundibulum that was thin walled. This cannot be enlarged by resection and mobilization of the parietal and septal insertions of the infundibular septum. In our opinion, it requires an enlarging patch through a ventriculotomy incision, which is similar to the incision used for the classic transventricular repair.

In the 98 patients who underwent transatrial repair, the mean right ventricular to left ventricular pressure ratio measured in the operating room after repair was 0.47, which was similar to the value of 0.56 for 391 patients who underwent classic transventricular repair at the same institution. Dr Dietl also found that this method provides satisfactory relief of pulmonary stenosis.

In our series, a limited transannular patch was placed in 26 patients, 26.5% of the group of 98. The criteria we use for transannular patching include intraoperative measurement of the pulmonary valve annulus and comparison of this value with normal values. In the series of Dr Dietl, a transannular patch was placed in 64% of the patients.

In our series, there were no early or late deaths and no reoperations, and each of the 109 patients was in New York Heart Association class I at follow-up. This is quite similar to the results Dr Dietl has presented.

I understood from the manuscript that this may not be a consecutive series of tetralogy repairs. Dr Dietl, what percentage of patients having repair during this time interval underwent a transatrial repair compared with a classic repair? Do you recognize contraindications to this approach? Because preservation of right ventricular function after repair has been demonstrated when a right ventriculotomy is avoided and a competent pulmonary valve remains, what criteria do you use for placement of transannular patches?

Finally, as long-term propranolol treatment had been employed in 8 patients, 2 of whom died, what is your current approach to patients already on a regimen of long-term propranolol therapy?

DR DIETL: I thank Dr Pacifico for his very kind comments. To answer his questions, only 1 patient underwent a transventricular approach during the same interval as this series, and that patient had tubular hypoplasia of the infundibulum. The infant died because a major right ventricular branch of the right coronary artery was injured, causing a massive right ventricular infarction. This deterred us from any further use of that approach. I think the transatrial approach is ideal. It can be used in nearly every instance except in the presence of severe tubular hypoplasia of the infundibulum, which is unusual.

The criteria for transannular patching are essentially the same as those of the Birmingham group. We use the Rowlatt tables to determine the appropriate size of the pulmonary annulus. We enlarge it without hesitation using a very limited infundibular incision so the pulmonary artery patch just barely goes across the annulus.

As far as propranolol is concerned, we do not prescribe it anymore. Some cardiologists are still using propranolol to delay repair until the patient is 2 years old. We disagree, because long-term treatment with propranolol can be deleterious to ventricular function, and also because several infants are still at risk for hypoxic spells. Early shunt or total repair is much safer.

Myocardial Salvage With Trolox and Ascorbic Acid for an Acute Evolving Infarction

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Both Trolox (a water-soluble analogue of α-tocopherol) and ascorbic acid were more effective than superoxide dismutase or catalase in protecting myocyte cell cultures from free radical attack (induced by hypoxanthine and xanthine oxidase). In a canine model of two hours of left anterior descending coronary artery occlusion followed by four hours of reperfusion, Trolox and ascorbic acid reduced the area of infarction within the area at risk. The Trolox group received 500 mL of deoxygenated saline solution containing 2.0 g of Trolox, 3.0 g of ascorbic acid, and 18 mg of EDTA (ethylenediaminetetraacetic acid) infused into the ascending aorta 30 seconds before and four minutes after reperfusion. Saline controls received 500 mL of deoxygenated saline solution containing 18 mg of EDTA. The angioplasty group had unmodified reperfusion by simple release of the occlusion. The area at risk and the area infarcted were estimated with Evans blue and triphenyl tetrazolium hydrochloride stains, respectively. The ratio of the area infarcted to the area at risk was significantly lower with Trolox (angioplasty, 30.4% ± 5.1%; saline, 20.8% ± 2.9%; and Trolox, 8.7% ± 4.0%; $p < 0.01$). In summary, the antioxidants Trolox and ascorbic acid effectively reduced myocardial necrosis after ischemia.

(Ann Thorac Surg 1989;47:553–7)

The advent of thrombolytic therapy and emergency angioplasty has focused cardiac research on interventions intended to limit infarct size in patients seen within four hours of an acute evolving infarction. The interventions that have been demonstrated to reduce infarct size include emergency coronary artery bypass grafting [1–3], circulatory assistance during emergency angioplasty [3–5], and either reducing myocardial metabolic demands [6] or infusing superoxide dismutase (SOD) and catalase during reperfusion [7].

Experimental studies have indicated that oxygen-mediated free radical injury [7–9] contributes to the myocardial damage associated with ischemia and reperfusion. Therefore, we compared the effectiveness of selected antioxidants in protecting canine ventricular myocytes from "pharmacologically" generated free radicals, and we evaluated the most effective scavengers in a canine model of regional myocardial ischemia and reperfusion intended to simulate a patient seen with an acute myocardial infarction.

We found that Trolox, a water-soluble analogue of vitamin E, and ascorbic acid were effective in preventing myocyte necrosis in cell culture studies and in a canine model of two hours of left anterior descending coronary artery (LAD) occlusion followed by four hours of reperfusion.

Material and Methods

Cell Cultures

Adult canine ventricular myocardium was dissociated with trypsin and collagenase. The supernatant was centrifuged to collect myocytes. After the supernatant was discarded, the cells were resuspended in culture medium containing 10% fetal bovine serum and Dulbecco's modified Eagle's medium (Gibco Laboratories, Life Technologies Inc, Grand Island, NY). The fibroblasts and myocytes were separated manually, and the identity of the myocytes was confirmed by the morphological appearance (Fig 1, left) and by fluorescent staining with antibodies to actin [10] (Fig 2, left) and to ventricular myosin light chain 1 [11] (Fig 2, right).

Myocyte cultures of the same generation and age were employed for these studies. The number of myocytes tested in each culture dish was $2.25 \pm 0.06 \times 10^5$ cells, which was similar for each experiment. The time to myocyte necrosis from a "pharmacological" free radical injury was used to compare the effectiveness of the antioxidants. The morphological criteria for myocyte necrosis were sarcolemmal rupture and cell shrinkage (Fig 1, right).

Free Radical Studies

The free radical studies were performed by removing the cell culture medium and adding 6.0 mL of phosphate-buffered saline solution (pH 7.4). Incubation (at 37°C) with phosphate-buffered saline solution alone did not produce any morphological changes for 45 minutes ($n = 10$). The addition of hypoxanthine (1 mmol/L) and xanthine oxidase (300 IU/L) rapidly produced myocyte necro-

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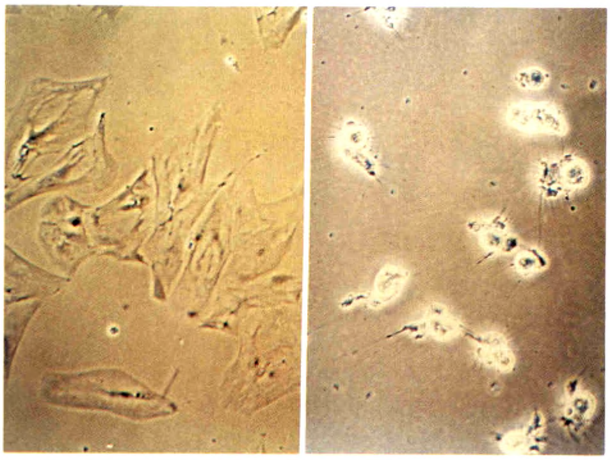

Fig 1. The morphological appearance of cultured canine myocytes in phosphate-buffered saline solution (left) and two minutes after the addition of hypoxanthine and xanthine oxidase to generate free radicals (right). The free radicals produced sarcolemmal rupture and cell shrinkage. (Magnification, ×200 before 53% reduction.)

sis (n = 10) (see Fig 1, right). The addition of hypoxanthine (n = 10) or xanthine oxidase (n = 10) alone did not induce any morphological changes at 15 minutes.

The substances evaluated for preventing free radical attack were Trolox, a water-soluble analogue of vitamin E (Aldrich Chemical Co, Milwaukee, WI); ascorbic acid (Hoffmann-La Roche, Brampton, Ont, Canada); SOD (Sigma Chemical Co, St. Louis, MO); and catalase (Boehringer-Mannheim, Montreal, Que, Canada). All antioxidants tested were administered immediately before the addition of the free radical generation system. The concentrations of each antioxidant were established from previous reports and from preliminary studies. We employed approximately twice the concentrations of SOD and catalase reported by Jolly and colleagues [7] to reduce myocardial infarct size by 50% in canine studies of regional ischemia (SOD = 14,500 IU/kg and catalase = 55,000 IU/kg).

Preliminary studies were performed to establish the optimal concentrations of Trolox and ascorbic acid to be tested. In myocyte culture studies, we found that Trolox concentrations of less than 1.34 mmol/L reduced the time to myocyte necrosis. Therefore, we used this concentration for both Trolox and ascorbic acid in our myocyte culture studies. The effect of preincubating the myocytes with Trolox and ascorbic acid in phosphate buffered saline solution, before the addition of the free radical generation system, was studied to determine the optimal protection times for these antioxidants.

Canine Studies

Mongrel dogs weighing 15 to 25 kg were anesthetized with sodium pentobarbital (30 mg/kg administered intravenously), intubated, and ventilated with a Harvard respirator. The animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

A median sternotomy was performed. Catheters were placed in the right femoral artery to monitor arterial pressure, and a micromanometer-tipped catheter was inserted into the left ventricle from the apex to monitor ventricular pressure. The LAD was isolated just distal to the first diagonal branch, and a 3 to 5 mm segment was dissected. The heart was carefully inspected, and any large collateral vessels from the right or circumflex coronary artery were reversibly ligated near the ventricular apex to provide a reproducible region of ischemia. A Doppler flow probe was placed around the LAD to confirm the absence of blood flow with ischemia and the restoration of blood flow with reperfusion in the LAD. The animals were randomly allocated to the three experimental groups: angioplasty group, saline group, and Trolox group.

In the angioplasty group (n = 8), the LAD was occluded for two hours. Then the occlusion was released, and the ischemic myocardium was reperfused for four hours to simulate emergency angioplasty in a patient seen within two hours of an acute coronary occlusion. In the saline group (n = 7), 500 mL of deoxygenated saline solution containing 18 mg of EDTA (ethylenediaminetetraacetic acid) at a pH of 7.4 was rapidly infused into the ascending aorta, beginning 30 seconds before reperfusion, at a rate of approximately 100 mL/min. The Trolox group (n = 6) also received 500 mL of deoxygenated saline solution containing 18 mg of EDTA, 2.0 g of Trolox (16 mmol/L), and 3.0 g of ascorbic acid (34 mmol/L) at a pH of 7.4.

Arterial pressures were maintained near control values during reperfusion by fluid infusions. The animals were killed with an anesthetic overdose, and the hearts were excised after four hours of reperfusion.

Determination of Area at Risk and Area of Infarction

The area at risk and the area of infarction were estimated by a dual-staining technique [7]. Evans blue (500 mL, 0.25%) was infused into the aortic root at a pressure of 80 mm Hg with the LAD occluded to assess the area at risk. At the same time, 500 mL of 1.5% triphenyl tetrazolium

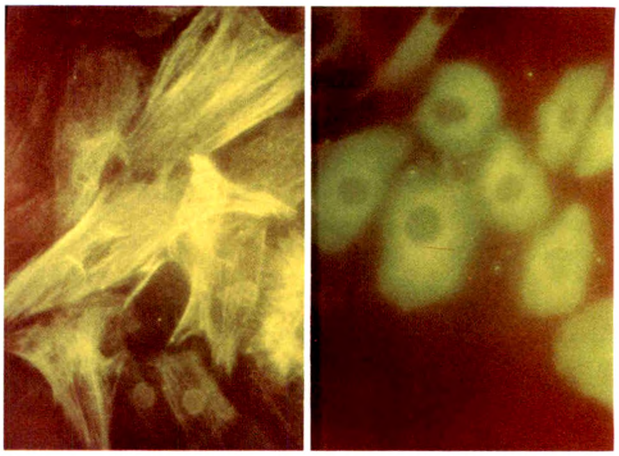

Fig 2. Cultured canine ventricular myocytes with fluorescent staining by antibodies to actin (left) and to ventricular myosin light chain 1 (right). (Magnification, ×200 before 53% reduction.)

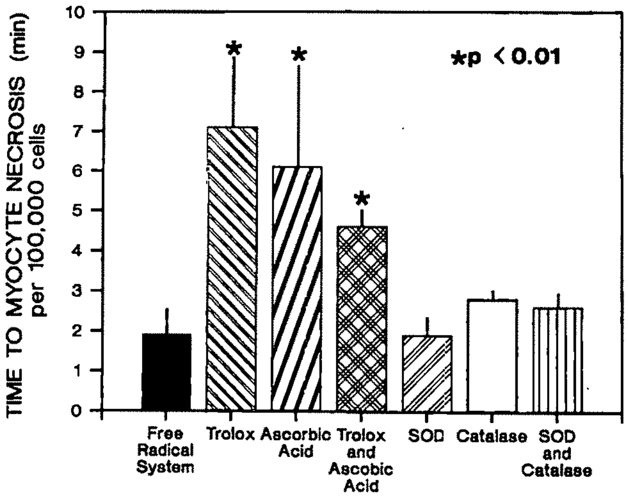

Fig 3. The time from the addition of hypoxanthine and xanthine oxidase (to generate free radicals) until myocyte necrosis (no preincubation with antioxidants). Free radical generation rapidly produced myocyte necrosis. Trolox, ascorbic acid, and the combination of the two prolonged the time to myocyte necrosis, but superoxide dismutase (SOD), catalase, and the combination of the two did not protect the myocytes from free radical injury.

hydrochloride was infused into the LAD distal to the site of occlusion at 37°C and 80 mm Hg to delineate the area of infarction. The left ventricle was cut into slices 1 cm thick, and the areas at risk (the regions that did not stain with Evans blue) and the areas of infarction within the area at risk (the regions that did not stain with triphenyl tetrazolium) were measured with a planimeter. The area of infarction was expressed as a percentage of the area at risk.

Statistical Analysis

Statistical analysis was performed with the Statistical Analysis System programs (SAS Institute, Cary, NC). Differences between times to myocyte necrosis and the areas of infarction were evaluated by an analysis of variance, and the differences were specified by Duncan's multiple range test when the *F* ratio of the analysis of variance was significant ($p < 0.05$). Canine hemodynamic measurements were assessed by a two-way analysis of variance (simultaneously evaluating time and treatment group), and differences were specified by a one-way analysis of variance and Duncan's test.

Results

Myocyte Cell Cultures

In control experiments with myocytes in phosphate-buffered saline solution but without hypoxanthine or xanthine oxidase, myocytes had no morphological changes until 45 minutes. The addition of either hypoxanthine or xanthine oxidase did not induce any morphological changes by 15 minutes. The addition of hypoxanthine and xanthine oxidase induced myocyte necrosis within three minutes (Fig 3; see Fig 2, left). The addition of Trolox (1.34 mmol/L), ascorbic acid (1.34 mmol/L), and the combination of Trolox (0.67 mmol/L) and ascorbic acid (0.67 mmol/L) significantly ($p < 0.01$) prolonged the time to myocyte necrosis (see Fig 3). However, the addition of SOD (24,200 IU/L), catalase (92,000 IU/L), or the combination of these at the same concentrations did not prolong myocyte survival after free radical generation (see Fig 3). Therefore Trolox and ascorbic acid were more successful than SOD and catalase in retarding free radical damage to the myocytes.

In preincubation studies, the antioxidant was preincubated before the addition of hypoxanthine and xanthine oxidase. The antioxidant effect of Trolox peaked with three minutes of preincubation and then decreased to control levels with seven minutes of preincubation, whereas that of ascorbic acid decreased linearly with increasing duration of preincubation and also approached control levels with seven minutes of preincubation. These results indicated that the times of optimal protection for Trolox and ascorbic acid differed, and suggested that some Trolox may need to be incorporated into the lipid membranes of the myocyte to be most effective.

Canine Study

Hemodynamic measurements were not different between groups before reperfusion. Occlusion of the LAD decreased left ventricular end-systolic pressure from 110 ± 33 mm Hg before occlusion to 96 ± 32 mm Hg after two hours of occlusion ($p < 0.01$) at similar left ventricular end-diastolic pressures (7 ± 2 mm Hg before occlusion and 8 ± 6 mm Hg after two hours of occlusion). Reperfusion decreased left ventricular end-systolic pressure in the angioplasty and saline groups but not in the Trolox group (at four hours of reperfusion: angioplasty group, 74 ± 29 mm Hg; saline group, 85 ± 20 mm Hg; Trolox group, 110 ± 25 mm Hg; $p < 0.01$). Reperfusion increased left ventricular end-diastolic pressure in the angioplasty group but not in the Trolox group (at four hours of reperfusion: angioplasty group, 11 ± 2 mm Hg; saline group, 9 ± 4 mm Hg; Trolox group, 5 ± 3 mm Hg; $p < 0.01$). The infusion of dopamine hydrochloride at 4 μg/kg/min restored left ventricular end-systolic pressure to

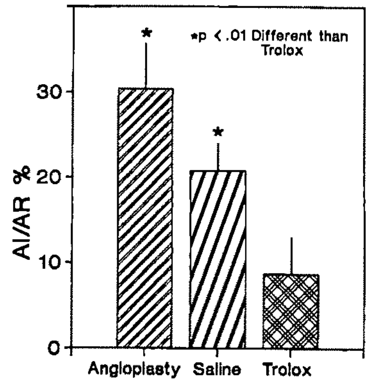

Fig 4. The area of infarction (AI) expressed as a percentage of the area at risk (AR) was significantly reduced with Trolox. An infusion of deoxygenated saline solution reduced the percentage of infarction compared with the angioplasty group, but the difference was not significant.

preischemic values in all groups, but the left ventricular end-diastolic pressure measurements remained different (angioplasty group, 14 ± 6 mm Hg; saline group, 11 ± 2 mm Hg; Trolox group, 5 ± 3 mm Hg; $p < 0.05$).

The area at risk as a percentage of the area of the left ventricle was not significantly different between the three groups (angioplasty group, 22.3% ± 3.1%; saline group, 20.8% ± 4.1%; Trolox group, 20.1% ± 2.0%). Figure 4 illustrates the area of infarction expressed as a percentage of the area at risk. Trolox significantly reduced the area of infarction within the area at risk. In addition, the saline group had a lower percentage of infarction compared with the angioplasty group, but the difference was not significant ($p = 0.051$).

Comment

Experimental studies have implicated oxygen-mediated free radical injury as an important mechanism of damage in the setting of ischemia and reperfusion [7–9]. The myocardial defenses against free radical injury include two types of antioxidants: preventive antioxidants, which convert potential sources of free radicals such as H_2O_2 into inert products, and chain-breaking antioxidants, which trap free radicals and prevent peroxidative damage. In biological systems, glutathione peroxidase and catalase are preventive antioxidants, whereas SOD, ascorbic acid, uric acid, bilirubin, reduced glutathione, and protein sulfhydryl groups are water-soluble chain-breaking antioxidants [12, 13]. Vitamin E is the major and possibly the only lipid-soluble chain-breaking antioxidant [14, 15].

Doroshow and colleagues [16] demonstrated that heart muscle contains only 27% of the SOD activity and less than 1.3% of the catalase activity found in the liver. Both heart and liver are equally active with respect to selenium-dependent glutathione peroxidase activity. Therefore, the heart muscle is not as well equipped to detoxify free radicals as the liver and may be more sensitive to "reperfusion" injury [16]. Guarnieri and colleagues [17] found that hypoxia decreases myocardial glutathione peroxidase and SOD activities, which persist for at least 60 minutes after reoxygenation. Das and associates [18] found that the activity of SOD, catalase, and glutathione peroxidase is decreased after ischemia. Therefore, myocardial free radical injury may be aggravated during reperfusion because the cellular defenses are diminished by ischemia and hypoxia.

Gauduel and Duvelleroy [19] demonstrated that α-tocopherol is a more effective antioxidant than SOD, catalase, reduced glutathione, or mannitol. They found that α-tocopherol is at least three times more effective than SOD and five times more effective than catalase in preventing malonaldehyde formation during reperfusion after global ischemia. Because α-tocopherol is lipid soluble, it cannot be given intravenously to patients with an acute myocardial infarction.

The ideal antioxidant to prevent myocardial free radical injury should be both water soluble and lipid soluble to facilitate diffusion into both the lipid and aqueous compartments and prevent membrane lipid peroxidation. Trolox (6-hydroxy-2,5,7,8-teramethyl-chroman-2-carboxylic acid, an antioxidant originally designed for food preservation [20]) has a structural resemblance to α-tocopherol but is both water soluble and lipid soluble. In vitro studies [21] have demonstrated that Trolox is an excellent antioxidant for inhibiting peroxidation in phospholipid bilayers. Although α-tocopherol traps peroxyl radicals more rapidly than Trolox in hydrocarbon solvents [22, 23], Trolox is much more soluble in water and is therefore able to rapidly equilibrate between the aqueous and lipid phases [24]. The much greater mobility of Trolox and its ready solubility in water mean that it can be quickly recruited and used at sites of lipid peroxidation when "local" defenses including, in particular, the membrane-bound antioxidant α-tocopherol have been overwhelmed by free radical attack.

Ascorbic acid has been demonstrated to be an effective water-soluble antioxidant [12, 21]. In addition, ascorbic acid can "regenerate" α-tocopherol and Trolox after their partial oxidation by free radicals to the tocopheroxyl or Trolox radicals, respectively [21, 25]. In this way, the membrane free radical is transported, in effect, from the lipid phase, which it could damage, out into the more or less inert aqueous phase [21, 25].

Both Trolox and ascorbic acid were more protective in the myocyte culture studies against a pharmacological free radical injury than SOD, catalase, or the combination of the two, despite the fact that we employed twice the concentrations recommended by Jolly and colleagues [7]. Because our preincubation studies appeared to reflect different action sites, we elected to use a combination of Trolox and ascorbic acid in our canine studies to optimize scavenger protection.

In our canine studies, Trolox and ascorbic acid were prepared in deoxygenated saline solution, and EDTA was added to chelate any iron present in the solution. Both Trolox and ascorbic acid are readily oxidized, and anaerobic conditions must be present to maintain their antioxidant activity. In addition, administration of these agents into the ascending aorta may prevent oxidation prior to their delivery to the myocardium.

We used the dual-staining technique described by Jolly and coworkers [7] to assess the extent of infarction within the region at risk. Previous studies from our laboratory [26] have shown that even one hour of reperfusion is sufficient to wash out the myocardial dehydrogenase enzymes required to convert tetrazolium to its red color. To confirm the adequacy of our staining technique, we performed electron microscopy on the areas that did and those that did not stain red with tetrazolium. The red areas had minimal disruption of cellular architecture, whereas areas without staining had marked deterioration of cellular architecture.

Trolox and ascorbic acid effectively reduced infarction in this canine model intended to simulate successful thrombolysis and emergency angioplasty in a patient seen within two hours of an acute LAD occlusion. An infusion of deoxygenated saline solution during reperfusion also reduced the area of infarction within the area at risk, although the difference was not significant. Previous studies in our laboratory [27] demonstrated that limiting the oxygen content of the initial reperfusate reduced the amount of necrosis of an isolated gracilis muscle that had been ischemic for 12 hours. The deoxygenated saline solution also contained EDTA, which may have reduced oxygen free radical formation by chelating iron. The combination of Trolox, ascorbic acid, and deoxygenated saline solution produced a 66% decrease in the myocardial infarction within the area at risk. This salvage is greater than has been reported with enzyme antioxidants. Our results suggest that an infusion of nonenzyme antioxidants during urgent revascularization may improve myocardial salvage with reperfusion.

In conclusion, the antioxidants, Trolox and ascorbic acid, prepared in a deoxygenated medium effectively prevented myocardial necrosis both in ventricular myocyte cell cultures and in a canine model of two hours of LAD occlusion followed by four hours of reperfusion. The infusion of these antioxidants during emergency revascularization may salvage jeopardized myocardium and reduce the infarct size in patients seen with an acute myocardial infarction.

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Composite Valve-Graft Replacement of Aortic Root Using Separate Dacron Tube for Coronary Artery Reattachment

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Traditional techniques of aortic root replacement have consisted of separate valve and graft replacement or use of a composite valve graft. These methods have been associated with problems including hemostasis, suture line disruption, and pseudoaneurysm development. They have had limited application in patients without sinus segment enlargement and acute aortic dissection. Between May 21, 1986, and September 7, 1988, 90 patients (73 male and 17 female) underwent replacement of the aortic valve and ascending aorta using a composite valve graft with reattachment of the coronary ostia using a separate, smaller (10 mm) Dacron tube graft. Aortic root replacement was done alone in 41 patients (46%), in association with a concomitant cardiac procedure in 26 patients (29%), and in 23 patients (26%) undergoing cardiac reoperation with and without a concomitant procedure. Aortic arch replacement was required in 25 patients (28%). Profound hypothermia and circulatory arrest were employed in 29 patients (32%). Early survival was 91% (82/90), and there were 4 late deaths. The procedure was found to be hemostatic (only 4 patients [4%] required reexploration for hemorrhage) and durable (no reoperation for pseudoaneurysm formation was necessary).

(Ann Thorac Surg 1989;47:558–65)

Major advances have been made in the surgical techniques used in patients requiring concomitant replacement of the aortic valve, tubular ascending aorta, and coronary sinus segment. Composite valve-graft replacement became a practical consideration with the operation described in 1968 by Bentall and DeBono [1] and later by Edwards and Kerr [2], which involved direct reattachment of the coronary artery origins to openings in an intraoperatively constructed valve-graft conduit. This is probably the most commonly utilized technique today for aortic root replacement. An alternative approach has been championed by others [3, 4]. In this approach, the supraannular portion of the sinus segment around the coronary arteries is preserved, and a separate valve and tube graft are inserted.

Problems encountered with these conventional techniques have been bleeding from the sites of reattached coronary artery origins, coronary artery distortion, and late development of pseudoaneurysms. These problems have been attributed to friable inadequate aortic tissue, particularly in the presence of Marfan syndrome, and to suture lines that are either under tension or inaccessible. Application of conventional methods is often limited in patients requiring aortic root replacement in the setting of acute aortic dissection in whom there has not been prior aortic dilation and in those undergoing cardiac reoperation.

In 1978, Cabrol and associates [5] introduced an alternative to direct coronary artery reattachment to a composite graft by employing a separate, smaller, transversely placed tube graft. In this report we present our experience with modifications of this latter technique in 90 patients who underwent aortic root replacement.

Material and Methods

Patient Population

Between May 21, 1986, and September 7, 1988, 283 patients required repair or replacement of the ascending aorta or aortic arch. A patch or primary repair was used in 13 (5%), simple graft replacement in 101 (36%), and a separate valve and graft in 60 (21%). A composite valve graft was employed in 109 (39%). In this last group, the coronary arteries were reconstituted by saphenous vein grafts in 5 and by direct reattachment using a button of aortic wall in 14 patients. A separate, smaller Dacron tube graft was used for coronary artery reattachment in 90 patients, and the technique and results of operation in these 90 patients constitute the material of this report.

There were 73 male patients (81%) with an average age of 51 years (range, 11 to 76 years) and 17 female patients (19%) with an average age of 43 years (range, 14 to 70 years). Operation was undertaken in 31 patients (34%) who had aortic dissection; acute dissection was present in 7 and chronic dissection in 24. In 59 patients (66%) there was medial degenerative disease without dissection. Sufficient clinical stigmata were present in 22 patients (24%) to classify them as having Marfan syndrome.

Isolated composite valve-graft replacement of the aortic root was employed in 41 patients (46%) (Fig 1). Chronic

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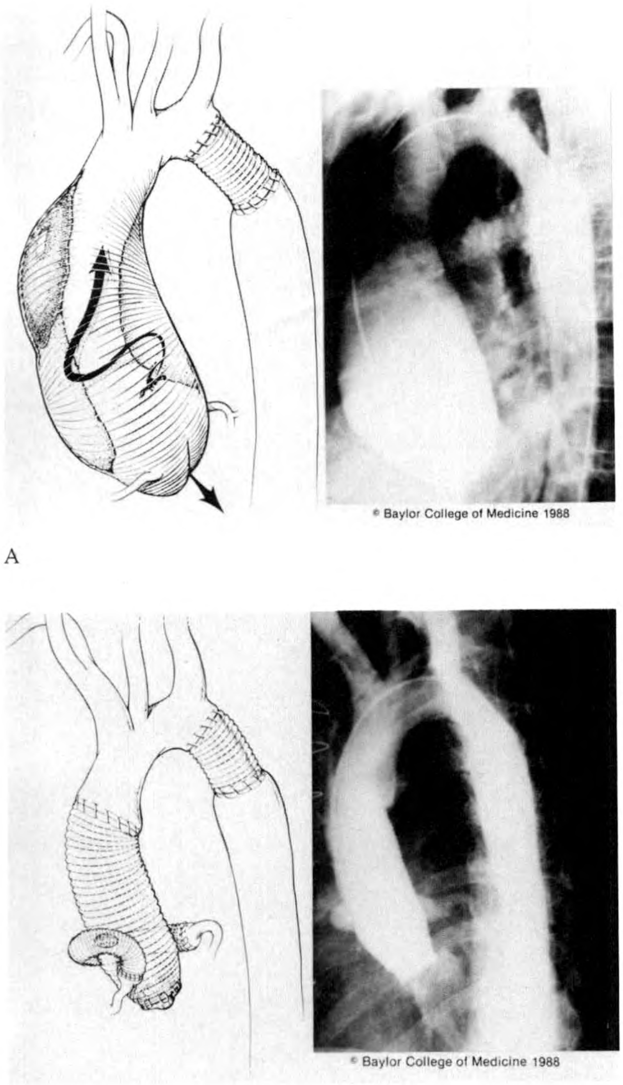

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Fig 1. *(A) Drawing and aortogram of patient with bicuspid aortic valve, aortic valve insufficiency, chronic dissection, and aneurysm of the ascending aorta. Note previous graft replacement for coarctation. (B) Drawing and aortogram made after operation using a modification of the procedure of Cabrol and co-workers [5] for aortic root replacement.*

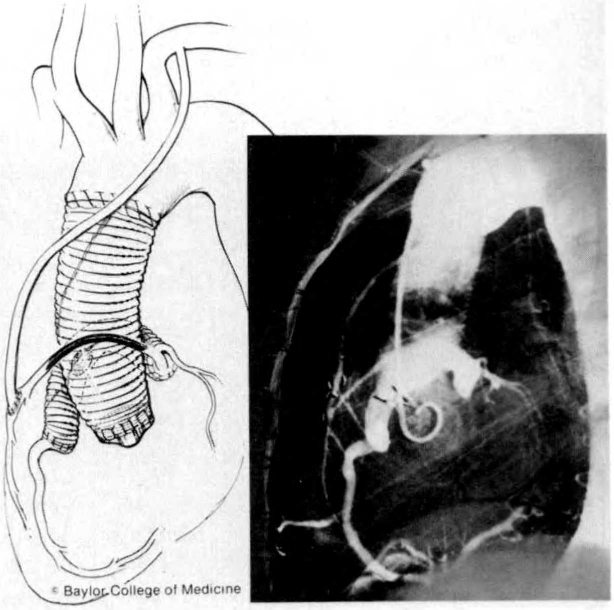

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Fig 2. *Drawing and aortogram of patient after operation using a modification of the procedure of Cabrol and co-workers [5]. The transverse coronary artery graft is widely patent, and the lesion in the left anterior descending coronary artery has been bypassed with the left internal mammary artery.*

aortic dissection was present in 5 of them; acute dissection, in 1; and Marfan syndrome, in 10.

Associated concomitant procedures were required in 45 patients (50%). These procedures included aortic arch replacement (with or without coronary artery bypass grafting) in 25, coronary artery bypass grafting in 14 (Fig 2), and a variety of other procedures in an additional 6 patients (Table 1). Among the 26 patients undergoing primary operation and a concomitant procedure, chronic dissection was present in 6 and acute dissection in 3. Twenty-three patients (26%) were undergoing a repeat operation, with or without a concomitant procedure, at the time of aortic root replacement; they had previously undergone one or more cardiac or proximal aortic operations. Among patients having a repeat operation, 13 had chronic aortic dissection and 3, acute dissection. Profound hypothermia and circulatory arrest were employed in 14 patients having primary operation for aortic arch replacement and in 15 patients having a repeat operation to replace the arch and/or to minimize difficult or hazardous dissection.

The reason for reoperation varied with the type and extent of the original procedures (Table 2). Two patients had undergone previous composite valve-graft replacement using the Bentall technique. A large false aneurysm arising from the left coronary artery reattachment developed in 1 of them, and in the other, a patient with Marfan syndrome, there was complete dehiscence of both coronary artery anastomotic sites and additional aneurysmal involvement of the remaining distal ascending and transverse aortic arch. Five patients had had previous place-

Table 1. Concomitant Procedures

Procedure	No. of Patients	Survival[a]
Arch replacement with or without coronary artery bypass grafting	25	23 (92)
Coronary artery bypass grafting	14	12 (86)
Mitral valve replacement	3	2 (67)
Aorta–right ventricular fistular repair	1	1 (100)
Atrial septal defect repair	1	1 (100)
Aorta–bifemoral bypass	1	1 (100)
Total	45	40 (89)

[a] Numbers in parentheses are percentages.

Table 2. Previous Cardiac and Aortic Root Operations

Operations	No. of Patients	Survival[a]
CABG	4	4 (100)
AVR with or without CABG	6	6 (100)
Aortoplasty, AVR, CABG	5	4 (80)
Ascending aortic graft with or without CABG and AVR	8	8 (100)
Total	23	22 (96)

[a] Numbers in parentheses are percentages.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting.

ment of an ascending aortic graft, and an aortic aneurysm proximal or distal to the graft and aortic valve insufficiency developed in all 5 (Fig 3). Two of them also had Marfan syndrome. There were 5 patients who had previously undergone aortic valve replacement and 4 who had had coronary artery bypass grafting; an aneurysm developed later in all 9. Aortoplasty, with or without aortic valve replacement, had previously been performed in 5 patients. Two additional patients with Marfan syndrome had had a previous cardiac operation, mitral valve replacement in 1 and aortic valve and separate ascending aortic graft replacement in the other. Sinus segment and distal aortic aneurysms developed in both patients. An additional 2 patients, both with Marfan syndrome, had undergone previous pectus excavatum repairs. Four patients had had two previous cardiac procedures, and 1 patient had had four procedures.

Operative Technique

Surgical treatment of all patients was based on modifications of the technique described by Cabrol and colleagues [5, 6] in which a composite valve graft is inserted and the coronary artery origins are reattached using a separate, smaller Dacron tube graft. Total cardiopulmonary bypass using bicaval cannulation and a femoral artery for pump return was employed whenever possible. In 2 patients,

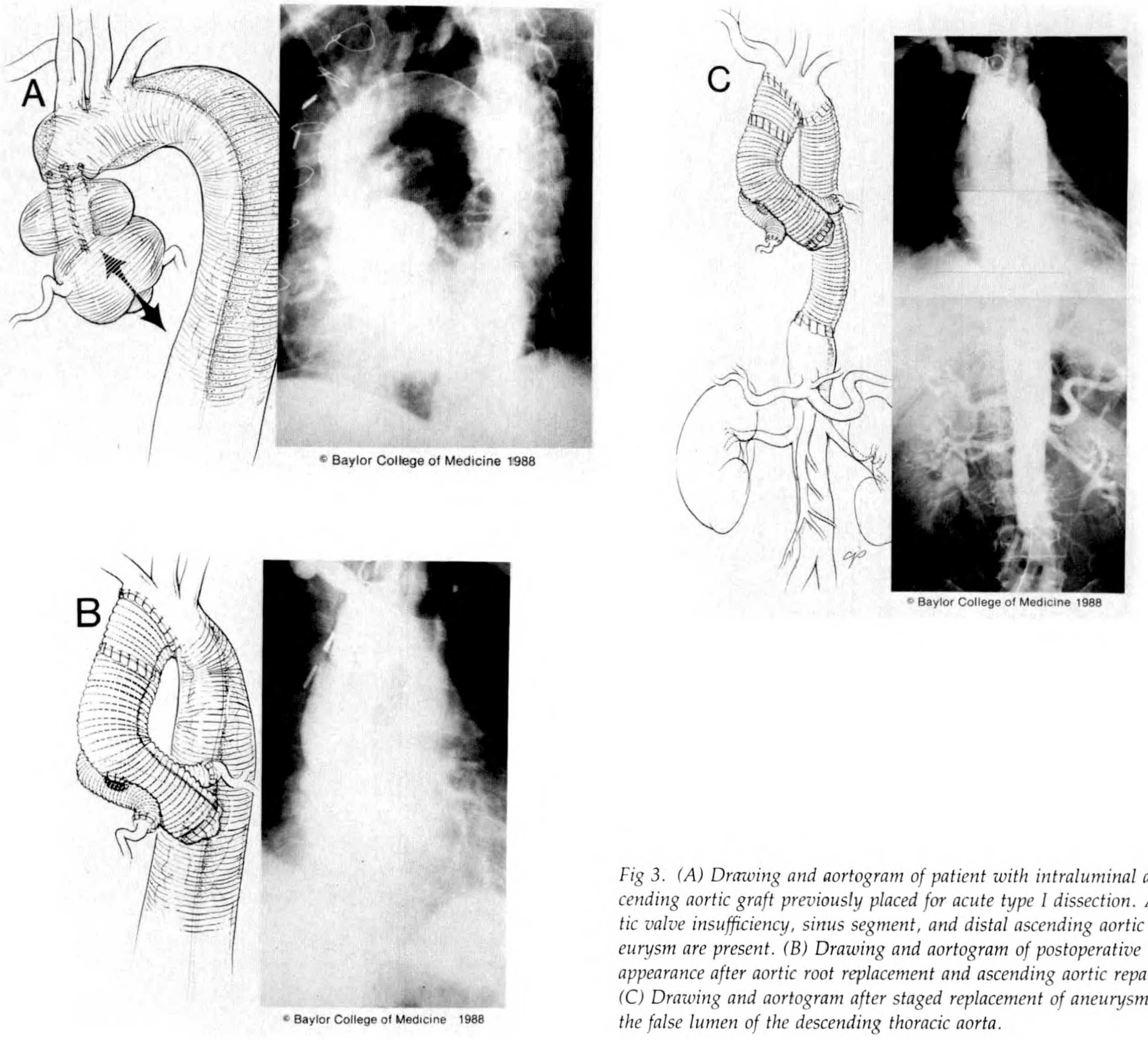

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Fig 3. (A) Drawing and aortogram of patient with intraluminal ascending aortic graft previously placed for acute type I dissection. Aortic valve insufficiency, sinus segment, and distal ascending aortic aneurysm are present. (B) Drawing and aortogram of postoperative appearance after aortic root replacement and ascending aortic repair. (C) Drawing and aortogram after staged replacement of aneurysm of the false lumen of the descending thoracic aorta.

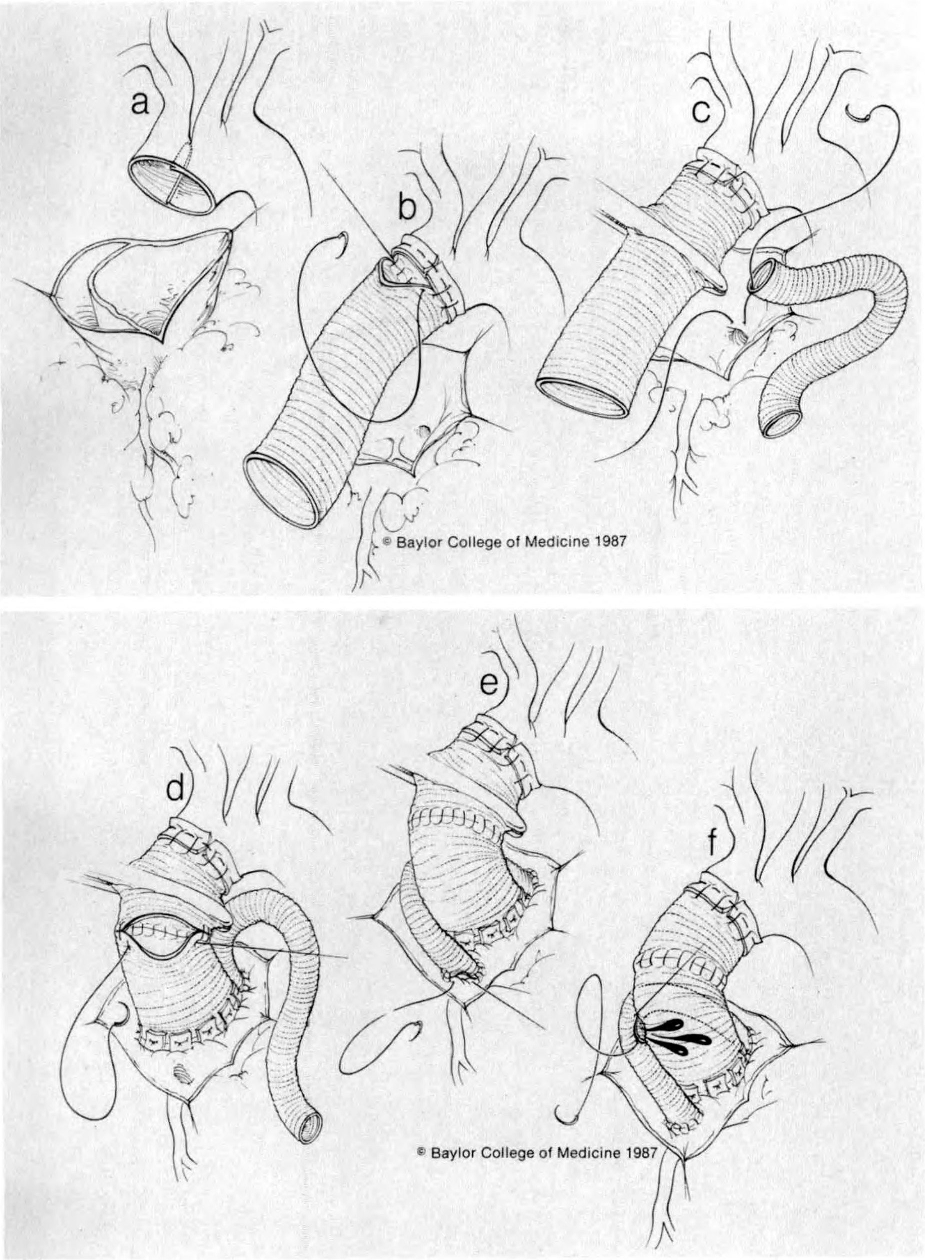

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Fig 4. Modification of the procedure of Cabrol and co-workers [5] using hypothermic circulatory arrest. (a–c) Distal anastomosis is performed without aortic clamp to replace maximum amount of ascending aorta. (d–f) After distal graft has been clamped and cardiopulmonary bypass resumed, a composite valve graft is inserted and the coronary artery origins are reattached to the aortic graft using a smaller, separate tube graft.

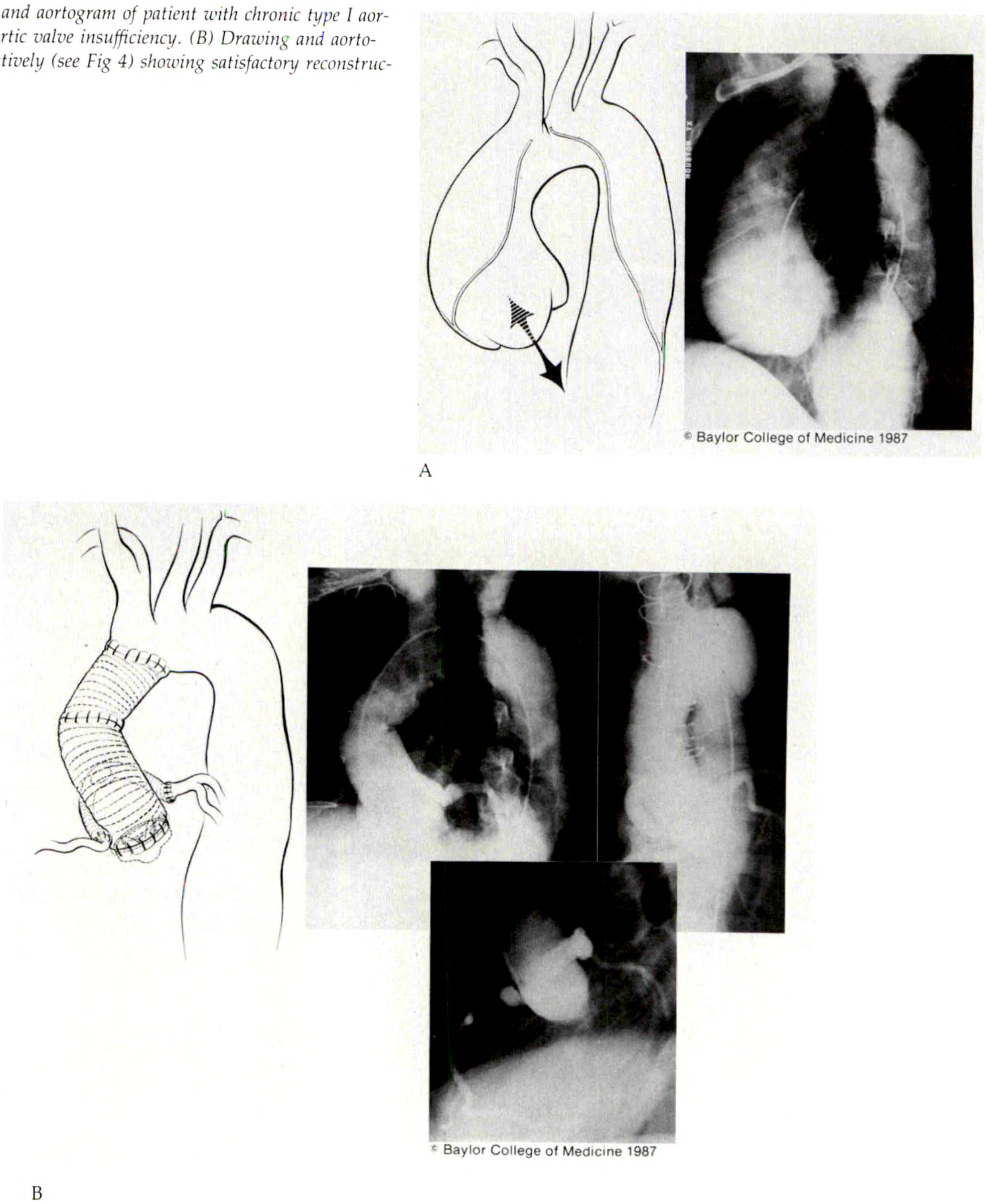
femoral vein–femoral artery partial cardiopulmonary bypass was used to produce deep hypothermia and allow circulatory arrest before the opening of the sternum in patients with large aneurysms who had undergone multiple previous operations. Hypothermic hyperkalemic dilute blood cardioplegia and topical hypothermia were used for myocardial preservation.

In patients requiring replacement of the aortic arch, in patients with acute aortic dissection, and in patients in whom safe distal aortic clamping was not feasible for anatomical reasons, profound hypothermia and circulatory arrest were used. In selecting the appropriate level of hypothermia at which to initiate a safe period of circulatory arrest, we continuously monitor the electroencephalogram and achieve electrocerebral silence before arresting the circulation [7].

A general description of the technique follows (Figs 4, 5). Cardiopulmonary bypass is established, and the ascending aorta is clamped as distally as possible. Alternatively the graft used to replace the transverse aortic arch is clamped just proximal to the innominate artery, and attention is directed to the aortic root. With the ascending aorta opened with a T incision, the aortic valve and sinuses are exposed. The coronary artery origins are identified, and cardioplegia is infused into each at regular intervals.

One end of a 10-mm woven Dacron tube graft, which has been coated with commercially available 5% albumin and autoclaved for three minutes at 270°F (133.28°C), is sutured end-to-end to the aortic wall surrounding the left main coronary artery using a continuous suture. Patency of this anastomosis can be confirmed and additional myocardial protection provided by administering more cardioplegic solution through this graft.

Fig 5. *(A) Drawing and aortogram of patient with chronic type I aortic dissection with aortic valve insufficiency. (B) Drawing and aortogram made postoperatively (see Fig 4) showing satisfactory reconstruction.*



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An appropriately sized St. Jude Medical composite valve graft is also saturated with 5% albumin and autoclaved to render the interstices of the graft impermeable to heparinized blood. The valve end of the graft is inserted into the aortic annulus using closely spaced pledgeted mattress sutures. The graft portion of the composite prosthesis is cut to the desired length and anastomosed end-to-end to the completely transected distal ascending aorta or to a previously placed distal graft. The smaller Dacron tube graft is passed to the right of the aortic graft, cut to an appropriate length allowing for a gentle craniad curve, and attached end-to-end to the aortic wall surrounding the origin of the right coronary artery. Repair is completed by creating a side-to-side anastomosis between the transversely placed coronary artery graft and the aortic portion, with the composite graft on the right anterior lateral surface of the latter, about 5 cm from the valve annulus.

Air is removed from the grafts and heart in a careful routine manner. We have found all suture lines to be accessible for securing hemostasis and, therefore, do not routinely tightly wrap the grafts with the aortic wall to achieve a dry field; rather, the aortic graft is loosely covered with redundant aneurysm wall to interpose tissue between it and the sternum. Because we have not relied on the inclusion technique for hemostasis, we have

Table 3. Results With Modification of the Cabrol Operation[a] in 90 Patients

Procedure	No. of Patients	Survival[b]
Aortic root reconstruction	41	38 (93)
Aortic root with associated procedures	26	22 (85)
Repeat aortic root with or without associated procedures	23	22 (96)
Total	90	82 (91)

[a] This refers to the operation of Cabrol and associates [5, 6]. [b] Numbers in parentheses are percentages.

not found it necessary to routinely create a fistula between the periprosthetic space and the right atrium. All patients are given oral Coumadin (crystalline warfarin sodium) for long-term anticoagulation.

Additional modifications are required in patients undergoing concomitant procedures or reoperation. For example, in patients in whom acute dissection destroys the origin of the right but not the left coronary artery, a small Dacron tube graft as described is interposed between the aortic graft and left coronary artery ostia, and continuity of the right coronary artery is achieved using a saphenous vein graft placed further distally on the coronary artery and taking the proximal end directly off the Dacron aortic graft. Severe distal coronary artery occlusive disease is bypassed with saphenous vein and internal mammary artery grafts in a routine manner, again with proximal anastomoses of vein grafts taken directly off the Dacron aortic graft. In patients undergoing reoperation, functioning saphenous vein bypass grafts are reattached to the aortic portion of the composite graft using buttons of aortic wall surrounding the proximal aortic anastomosis. When mitral valve replacement is required concomitantly, it can be accomplished through the aortic valve annulus, thereby avoiding a separate atrial incision [8].

Results

Early Results

The overall early (30-day or hospital) survival was 91% (82/90) (Table 3). Three early deaths occurred in patients undergoing primary operation and isolated composite valve-graft insertion. There were 4 early deaths among the 26 patients undergoing primary operation and concomitant operations; 2 of the 4 patients had coronary artery bypass grafting and 1 each, mitral valve replacement and arch replacement. The remaining early death was in a patient having a reoperation for chronic dissection. Five years previously, this patient had undergone graft replacement of the ascending aorta for acute aortic dissection and subsequently required aortic root and arch replacement.

Four of the early deaths were due to congestive heart failure. All 4 patients had had New York Heart Association functional class III or IV symptoms preoperatively. One of them underwent heart transplantation 3 days after operation and died 17 days later. Three deaths were the result of cardiac arrhythmias, all in patients with a preoperative history of arrhythmias. One early death was due to rupture of a dissecting thoracic aortic aneurysm 20 days after operation and after hospital discharge, before planned second-stage repair. Autopsy information was available on 5 patients; in each, the composite valve graft was satisfactory with all suture lines intact and all grafts patent. Among the 31 patients with aortic dissection, there were 30 early survivors (97%). Among the 59 patients without dissection, there were 52 early survivors (88%).

Perioperative bleeding problems were few; only 4 patients (4.4%) had to be returned to the operating room because of hemorrhage. In only 1 patient was it necessary to wrap the graft for hemostasis and create a fistula to decompress the perigraft space. Six patients were successfully operated on without transfusion of blood or blood products.

Additional early postoperative complications included transient focal neurological deficits, none of which were permanent, in 4 patients. Intraaortic balloon pump support was necessary in 3 (3.4%) of the 88 operative survivors. Heart block necessitating a permanent pacemaker and tracheostomy for prolonged respiratory support occurred in 2 patients each. There were two cases of sepsis, which were treated with 6 weeks of intravenously administered antibiotics.

Postoperative aortography was performed in 42 (51%) of the surviving patients before hospital discharge or on return for a second-stage distal aortic operation. In all 42, the proximal and distal anastomoses were intact, all transverse Dacron coronary artery grafts were patent, and there were no pseudoaneurysms at any sites.

Late Results

Follow-up information was available on all survivors either by physical examination or by correspondence directly with the patient using a standardized questionnaire or with the referring physician. There were 4 late deaths. Two were due to renal failure, 1 was due to myocardial infarction, and 1 was sudden and of unknown causes. One patient requiring hemodialysis died of progressive renal failure 3 months after composite valve-graft replacement of the aortic valve and ascending aorta, as well as arch replacement and reattachment of four previously placed coronary artery bypass grafts. The second patient who died of renal failure did so 2 months after a second-stage operation involving graft replacement of the descending thoracic aorta. A 70-year-old man died of a myocardial infarction 6 months after composite valve-graft replacement and coronary artery bypass grafting to four distal coronary arteries with saphenous vein grafts.

Late morbidity involved transient ischemic attacks in 3 patients, one episode in each of the patients, which resolved completely in all 3 in less than 24 hours. Hepatitis developed in 2 patients, both of whom recovered. One patient who had undergone composite valve-graft replacement of the aortic valve and ascending aorta for acute type I dissection and concomitant double coronary artery bypass grafting for occlusive coronary artery disease was later taken off Coumadin in preparation for a craniotomy for an intracerebral aneurysm. Once this patient with diffuse coronary artery occlusive disease was no longer on a regimen of anticoagulants, thrombosis of the small Dacron graft to the left main coronary artery developed, resulting in an anterior myocardial infarction. Protected by the distal saphenous vein grafts, the patient recovered.

No patient to date has required reoperation for problems related to the aortic root reconstruction using the technique described. Subsequent operations have included descending thoracic aortic aneurysm repair in 5 patients (1 death), thoracoabdominal aortic aneurysm repair in 1, muscle flap closure of the sternum in 1 patient who originally was seen with a sternal infection, abdominal aortic aneurysm repair in 1, carotid endarterectomy in 1, lymph fistula repair in 2, appendectomy in 1, and successful craniotomy for tumor in 1.

Comment

Composite valve-graft replacement of the aortic valve and ascending aorta has become a generally accepted surgical technique for treatment of aneurysmal involvement of the sinus segment with aortic valve insufficiency. Other indications include dissection and select cases of infection and reoperation. The most commonly employed procedure, originally described by Bentall and DeBono [1] in 1968, involves direct reattachment of the coronary artery origins to openings in a composite graft inserted using an inclusion technique, followed by wrapping the diseased aortic wall around the graft to achieve hemostasis. This approach was a major contribution because it allowed complete aortic root replacement with a reduced incidence of major hemorrhage. Nevertheless, employment of this technique has been associated with its own inherent limitations and difficulties [9–13].

With the use of the Bentall technique, hemorrhage at the time of insertion is primarily related to problems associated with coronary artery reattachment [14]. When the inclusion technique is used for composite valve-graft placement, there are virtually always overlapping and inaccessible suture lines. In addition, in annuloaortic ectasia, the coronary origins are displaced both distally and laterally from their normal anatomical position, thus necessitating tension when they are reattached to the graft.

Early bleeding was not a major problem in our experience with the modifications of the procedure introduced by Cabrol and co-workers [5, 6]. Only 4 patients (4%) needed reoperation for bleeding, 6 required no blood transfusions at all, and only 1 required a perigraft wrap and left-to-right fistula for hemostasis. In a review of 100 patients, Cabrol and colleagues [15] reported a similar experience with only 4 patients requiring reoperation for bleeding. Their group routinely employs graft wrapping to control bleeding and a fistula between the aortic wrap and the right atrial appendage to decompress the perigraft space. We attribute improved hemostasis to better exposure during suture placement, accessible suture lines, and elimination of tension on the coronary anastomosis with the use of the interposed Dacron graft.

Pseudoaneurysm formation after direct reattachment of the coronary arteries to a composite graft has been well documented [10–12]. This complication has been attributed to suture line tension due to anatomical factors related to the aortic root pathological condition being treated, or to the accumulation of blood under pressure within the aneurysm wrap of the graft creating tension on the coronary ostial reattachment suture lines. Development of perigraft hematoma can also lead to supravalvular graft stenosis with immediate hemodynamic consequences.

Kouchoukos and associates [16] studied by arteriography before hospital discharge 17 patients in whom the inclusion technique had been used, and found pseudoaneurysm formation at the coronary ostial anastomosis in 4. Stenosis of the left coronary ostium was noted in an additional patient. In late follow-up, they were able to identify 3 patients with pseudoaneurysm formation on aortograms made from 1 month to 69 months after hospital discharge. One patient underwent successful reoperation before hospital discharge, and 7 others were operated on from 3 to 69 months postoperatively (mean, 41 months), with 4 survivors.

Others [9, 10, 12, 13] have reported similar experiences with pseudoaneurysm formation in 7% to 25% of patients. Cabrol and colleagues [15] reported on 25 patients who were reinvestigated by cardiac catheterization and angiography between 1 month and 5 years after operation to determine the long-term results of their approach. In all patients, they found a satisfactory appearance of the prosthesis, no pseudoaneurysm formation, and no stenosis at the junction of the coronary tube and the coronary ostia. We investigated by root aortography 42 (51%) patients surviving operation, 41 before hospital discharge and 1 at 5 months postoperatively. In this larger group of patients studied in the early postoperative period, there were no pseudoaneurysms, tube graft occlusions, or coronary stenoses.

The inadequacies of the conventional approach to aortic root replacement are most obvious in circumstances not allowing for ease of coronary ostial graft reattachment. In many reoperations, friable, immobile aortic tissue surrounding the coronary artery origins can present almost insurmountable technical difficulties when direct reattachment is attempted. Another obstacle is encountered when there has been failure of the coronary artery ostia to migrate a distance from the aortic valve annulus that is compatible with ease of reattachment [17, 18]. This occurs when the aortic wall in the coronary sinus between the ostia and annulus is not involved in the expansion of the aneurysm. Both circumstances can produce troublesome intraoperative bleeding and late pseudoaneurysm formation. Use of a separate, smaller Dacron tube for coronary artery reattachment is applicable in both of these situations, ie, when the ostia and valve annulus are normally related and in a reoperation where there is limited tissue mobility. This is evidenced by 23 (26%) of our patients undergoing a reoperation without an increase in mortality or morbidity related to the technique (see Table 3).

Aortic root replacement using a composite valve graft and a separate, smaller Dacron tube to bridge the aortic graft and coronary ostia is simple and safe, and can be accomplished with excellent operative mortality and morbidity in a wide variety of aortic pathologies. Importantly, compared with classic techniques, operative hemorrhage is greatly reduced, and early development of pseudoaneurysm formation at the coronary artery reattachment site is virtually eliminated.

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Cryoablation of Septal Pathways in Patients With Supraventricular Tachyarrhythmias

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Eighteen patients with supraventricular tachycardia refractory to medical therapy underwent preoperative electrophysiological study and subsequent operation. There were 6 female and 12 male patients ranging in age from 1.5 to 31.6 years (mean age, 11.9 ± 7.8 years). Eleven had classic Wolff-Parkinson-White syndrome with intermittent tachycardia, and 7 had a form of permanent junctional reciprocating tachycardia. Five had impaired left ventricular function preoperatively. The location of the accessory conduction pathway was anteroseptal in 3, posteroseptal in 12, and both anteroseptal and posteroseptal in 3 patients. Pathway location was confirmed by intraoperative mapping in all patients. The pathways were ablated utilizing a cryoprobe at −70°C. All patients survived the operation, had immediate abolishment of delta waves and tachycardia, and were considered cured at the time of hospital discharge. Sixteen (89%) remain cured at a mean follow-up of 16.9 months. One patient with a posteroseptal pathway no longer has a delta wave but has had poorly documented episodes of tachycardia and is taking medication. One other patient with both anteroseptal and posteroseptal pathways had a recurrent delta wave 6 months postoperatively but has had no tachycardia and is asymptomatic without medication. No patient experienced heart block. Ventricular function has returned to normal in all 5 patients with impaired function preoperatively. Cryoablation is an effective method of abolishing accessory conduction pathways located in the anteroseptal or posteroseptal region. The method is easy, and results are comparable with those of other techniques previously described.

(Ann Thorac Surg 1989;47:566–8)

Since 1969 when successful surgical treatment of supraventricular tachycardia associated with Wolff-Parkinson-White syndrome was reported by Sealy and colleagues [1], numerous advances have been made in both the diagnosis and surgical correction of tachyarrhythmias. Most supraventricular arrhythmias are now easily identified by electrophysiological mapping techniques and can be cured by operative intervention.

The most common supraventricular tachyarrhythmia in children is that associated with Wolff-Parkinson-White syndrome. Interruption of the accessory conduction pathway as described by Sealy and colleagues [1] results in cure of the reciprocating tachycardia [2, 3]. The classic endocardial approach with surgical dissection of the left free wall, the right free wall, and the anteroseptal and posteroseptal regions remains the "gold standard" of surgical ablative techniques [4]. Guiraudon and coworkers [5] combined epicardial dissection and creation of cryolesions to produce similar results. The production of localized cryolesions in the region of the accessory conduction pathway has also been used with good success in the pediatric population [6]. We report here our initial experience with cryoablative therapy for septal pathways in the treatment of supraventricular tachyarrhythmias in a relatively young group of patients.

Material and Methods

Patient Population

From January 1985 to September 1988, 45 patients underwent operation at Medical University of South Carolina for supraventricular tachycardia associated with accessory conduction pathways. Eighteen of these patients had pathways localized to the anteroseptal or posteroseptal region, or both regions, and this group is the subject of this report.

There were 12 male and 6 female patients. Age ranged from 1.5 to 31.6 years with a mean of 11.9 years. The average age at onset of the arrhythmia was 4.6 years. Signs and symptoms at onset included palpitations in 8, syncopal episodes in 6, dyspnea in 3, cyanosis in 4, and tachycardia in 1. Previous cardiac medications included the following: atenolol, verapamil hydrochloride, procainamide hydrochloride, metoprolol tartrate, propranolol hydrochloride, lidocaine hydrochloride, digoxin, amiodarone, quinidine sulfate, and captopril. All had been unsuccessful in controlling the tachyarrhythmias. The average number of hospitalizations before the operation was two.

All patients underwent preoperative electrophysiological mapping. Eleven patients had classic Wolff-Parkinson-White syndrome with intermittent tachycardia, and 7 had permanent junctional reciprocating tachycardia. Twelve patients were found to have posteroseptal pathways, 3 had anteroseptal pathways, and 3 had both anteroseptal and posteroseptal pathways. Five patients had impaired left ventricular function preoperatively.

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Operative Technique

Through a median sternotomy incision, ventricular reference electrodes were placed on the right ventricle, and a clip-on quadripolar reference and pacing electrode was placed on the right atrial appendage. Detailed epicardial mapping was then carried out using a mobile mapping probe to identify the point of earliest depolarization on the ventricular side of the atrioventricular groove during atrial pacing and on the atrial side during ventricular pacing or supraventricular tachyarrhythmia.

After this, the aorta and both venae cavae were cannulated, and the patient was placed on cardiopulmonary bypass and maintained at normothermia. Caval tapes were tightened, ventricular fibrillation was induced, and a right atriotomy was made. A patent foramen ovale was sought and, if present, closed. The heart was then defibrillated.

Endocardial cardiac mapping was carried out around the tricuspid valve annulus. With a cryoprobe at −70°C placed for 90 to 120 seconds, cryolesions were produced beginning at the point of earliest activation. Frequently the delta wave was abolished with the initial lesion. Additional overlapping lesions were produced progressing toward the atrioventricular node until prolongation of the P-R interval or transient atrioventricular block occurred. At that point, several additional lesions were placed on the opposite side of the initial lesion. The patient was then checked for retrograde conduction with ventricular pacing, and if none was present, this and the abolishment of the delta wave were considered evidence of successful ablation of the accessory pathway. The right atriotomy was closed and cardiopulmonary bypass was discontinued.

Results

Of the 18 patients treated with cryoablation, 11 had classic Wolff-Parkinson-White syndrome confirmed preoperatively by electrophysiological studies. Seven patients had permanent junctional reciprocating tachycardia. Cryoablation of suspected accessory conduction pathways resulted in an immediate success rate of 100% as judged by abolishment of the delta wave, the retrograde conduction, and the tachycardia. There were no operative deaths. No second-degree or third-degree atrioventricular block occurred.

An 11-year-old boy (the fourth patient in this series) with cardiomyopathy and supraventricular tachyarrhythmias secondary to a posteroseptal pathway required early reoperation. At the initial procedure, intracardiac mapping was not as precise as desired, and cryolesions were placed at the coronary sinus and approximately 30 degrees around the circumference of the atrioventricular groove. Two hours postoperatively, the supraventricular tachycardia recurred, and he was returned to the operating suite. Repeat mapping revealed the area of earliest activation to be just lateral to the mouth of the coronary sinus. Multiple cryolesions were then produced with a cryoprobe at −70°C applied for up to 120 seconds. Two lesions at the mouth of the coronary sinus directed down toward the annulus of the tricuspid valve appeared to completely abolish the arrhythmias. No retrograde conduction could be detected, and an arrhythmia could not be induced with premature stimuli. The patient did well postoperatively, and has since remained in sinus rhythm without medication. In addition, the cardiomyopathy has resolved.

Two patients whose operations were considered failures live at some distance from South Carolina and have not returned for restudy. One of them, who had a posteroseptal pathway, was initially considered cured. He no longer has a delta wave but has had poorly documented episodes of tachycardia and is on a regimen of Dilantin (phenytoin) and tocainide hydrochloride. The other patient had both anteroseptal and posteroseptal pathways and also was considered cured at discharge. Six months postoperatively, he was noted to have a recurrent delta wave. He has had no tachycardia and is taking no medication. Documentation of recurrence in these 2 patients is incomplete at best, but for statistical purposes, they are considered failures. Thus 16 (89%) of the patients are completely cured at a mean follow-up of 16.9 months.

Transient postoperative pancreatitis developed in 1 patient who had a completely successful operation. It subsequently resolved with conservative measures. Another patient had transient mild neurological findings, which cleared. Heart block developed in no patient. Ventricular function returned to normal in all 5 patients who had depressed function preoperatively.

Comment

Surgical treatment of supraventricular arrhythmias, of which Wolff-Parkinson-White syndrome is the most common, has now advanced to the point that it is considered the therapy of choice in the majority of patients [7]. Since the original work by Sealy and colleagues [1], techniques in treating these potentially lethal forms of arrhythmias have been refined. This is particularly true with respect to the septal pathways. Early results with surgical dissection of septal pathways were not as satisfactory as those for free wall pathways. The anatomy of this region has since been well described [8], and Cox and associates [4] and others have obtained excellent results utilizing the dissection techniques described by Sealy and associates [1].

Several alternative approaches to the septal pathways have been suggested. Guiraudon and co-workers [5] have advocated the epicardial approach combined with cryolesions. Their results are similar but not superior. We and others [6] have been successful with combining precise intraoperative mapping and cryoablation.

We continue to use the endocardial approach combined with dissection for the management of pathways in the left and right free wall regions, even in small children. The use of a hand-held cryoprobe to produce precisely localized lesions in the region of accessory conduction pathways localized in the septal region is simple and avoids the need for surgical dissection in these spaces. We do not promote the use of the cryoprobe as a "superior technique," but we do believe it may have some advantages, especially in small children. It is an alternative to be considered.

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REVIEW OF RECENT BOOKS

Management of Esophageal Disease

Edited by David B. Skinner and Ronald H. R. Belsey
Philadelphia: W.B. Saunders, 1988
895 pp, illustrated, $145.00

Reviewed by Thomas W. Shields, MD

Doctor Skinner and Mr Belsey, both surgeons with extensive experience and interest in esophageal diseases, have put forth a comprehensive text on the diagnosis, evaluation, and management of disorders of this structure. The style is concise and in most part as objective as possible for two individuals who have personally done so much to advance the state of the art of surgery in this field. Reading of the preface and the chapter on the philosophy of esophageal surgery is a must. Their views on the place of surgical intervention, the training of esophageal surgeons, and the reasons for selection of the various operative procedures are succinctly forwarded for the reader's enlightenment. Moreover, the Churchillian phrases are delightful to read in what normally would be considered a dry surgical text.

The volume is divided into 12 sections: The Normal Esophagus, Investigation of Esophageal Disease, Principles of Medical Treatment, Principles of Surgical Treatment, Congenital Abnormalities, Neuromuscular Disorders, Hiatal Hernia and Reflux, Benign Strictures, Neoplasms, Trauma, Esophageal Varices, and Future Developments. The topics covered in each section are appropriate and the coverage is authoritative. Unfortunately, at times the material presented is quite opinionated, but then this is what one should expect from two such eminently qualified surgeons in the field. This is particularly evident in their discussion of malignant tumors of the esophagus. Doctor Skinner's en bloc resection is well presented, but it is doubtful that most would agree that this is the only acceptable curative procedure for carcinoma of the esophagus. A 5-year actuarial survival of 17% in a highly select group of patients is really not too much greater than a "real," as opposed to an "actuarial," survival of 12% following "palliative resection" of almost all comers (76% resection rate) to the Bristol Center reported by Mr Belsey in the succeeding chapter. It is here, too, in the section on esophageal tumors that much of the Japanese experience is ignored and no mention of the well-supported proposed Japanese staging system for esophageal carcinoma is made.

In this book on the esophagus, the inclusion of the management of the various disorders of the diaphragm, which the authors describe as "that neglected hinterland between the thorax and abdomen," adds little to the volume's worth, except in presenting the association between hiatal hernia and gastroesophageal reflux.

Overall, however, the text is a valuable source of information and guidance for all those interested in the management of esophageal diseases. The presentations are clear, the illustrations excellent, and the references replete with both fundamental older contributions and the more recent ones that have led to our greater understanding of this organ, which the authors call "the 'Cinderella' of medicine and surgery."

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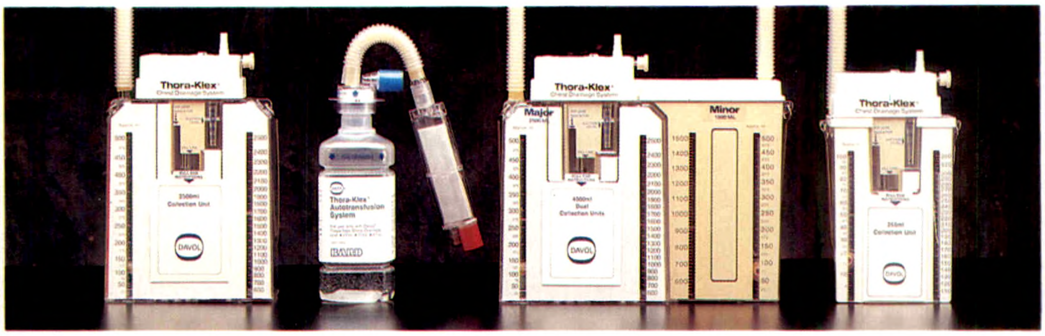

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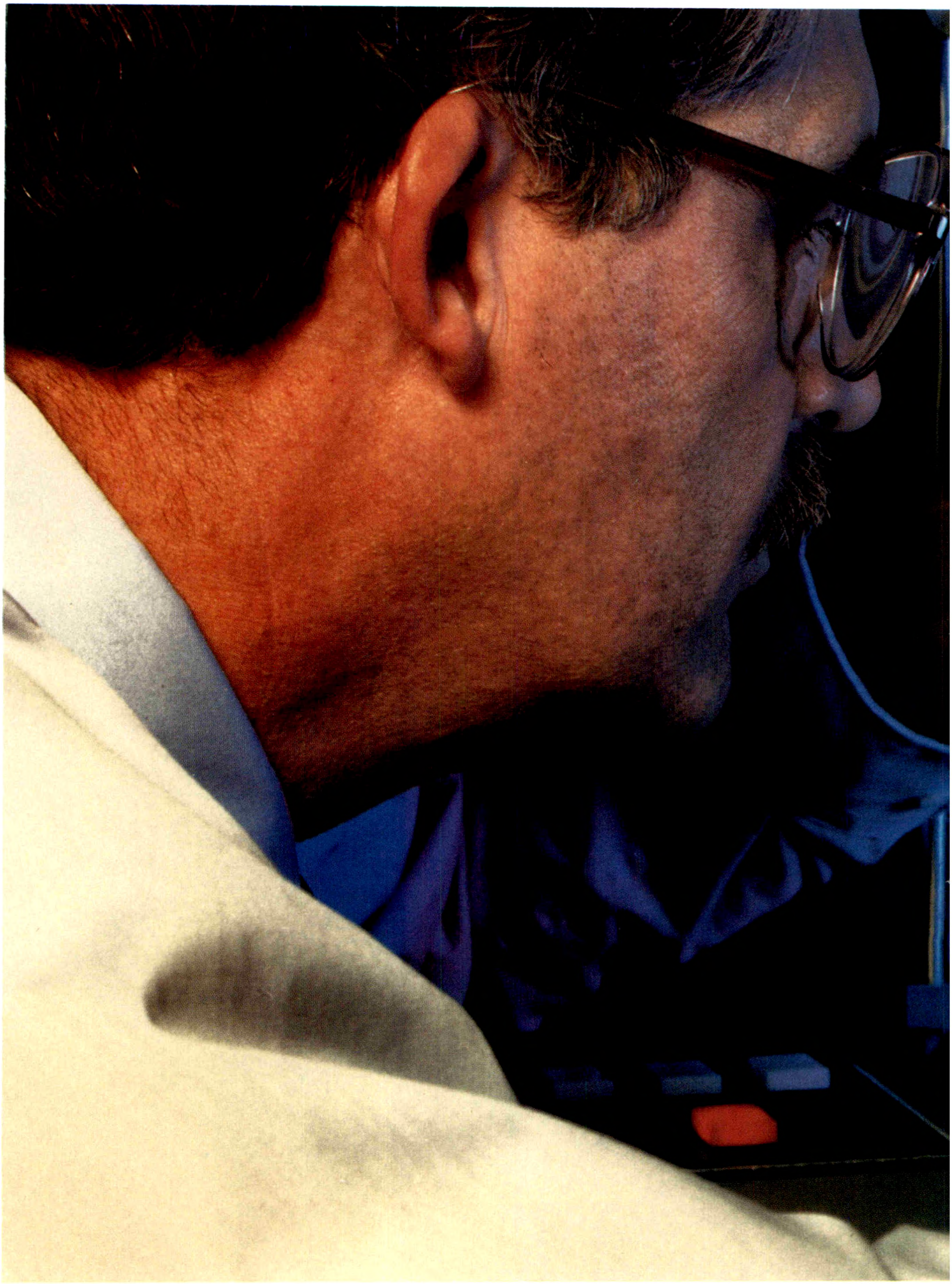

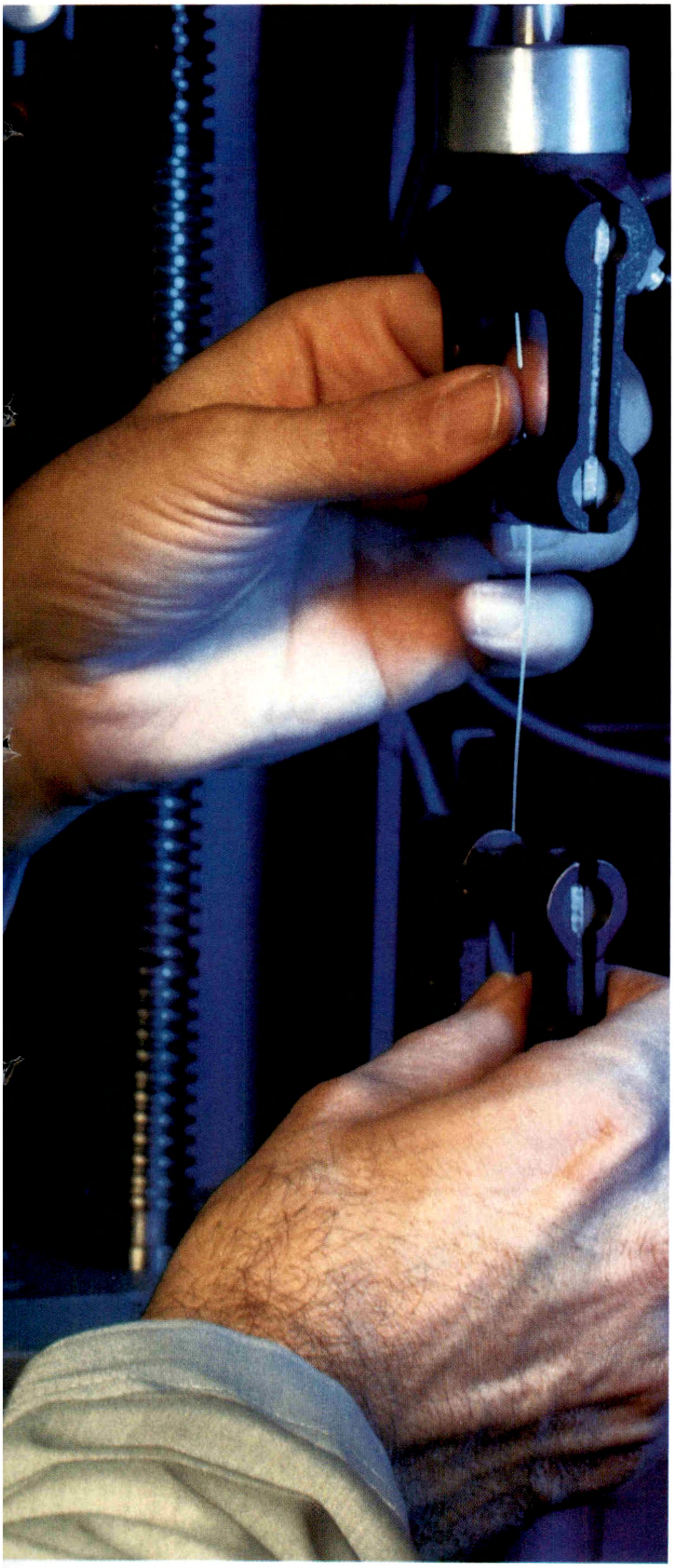

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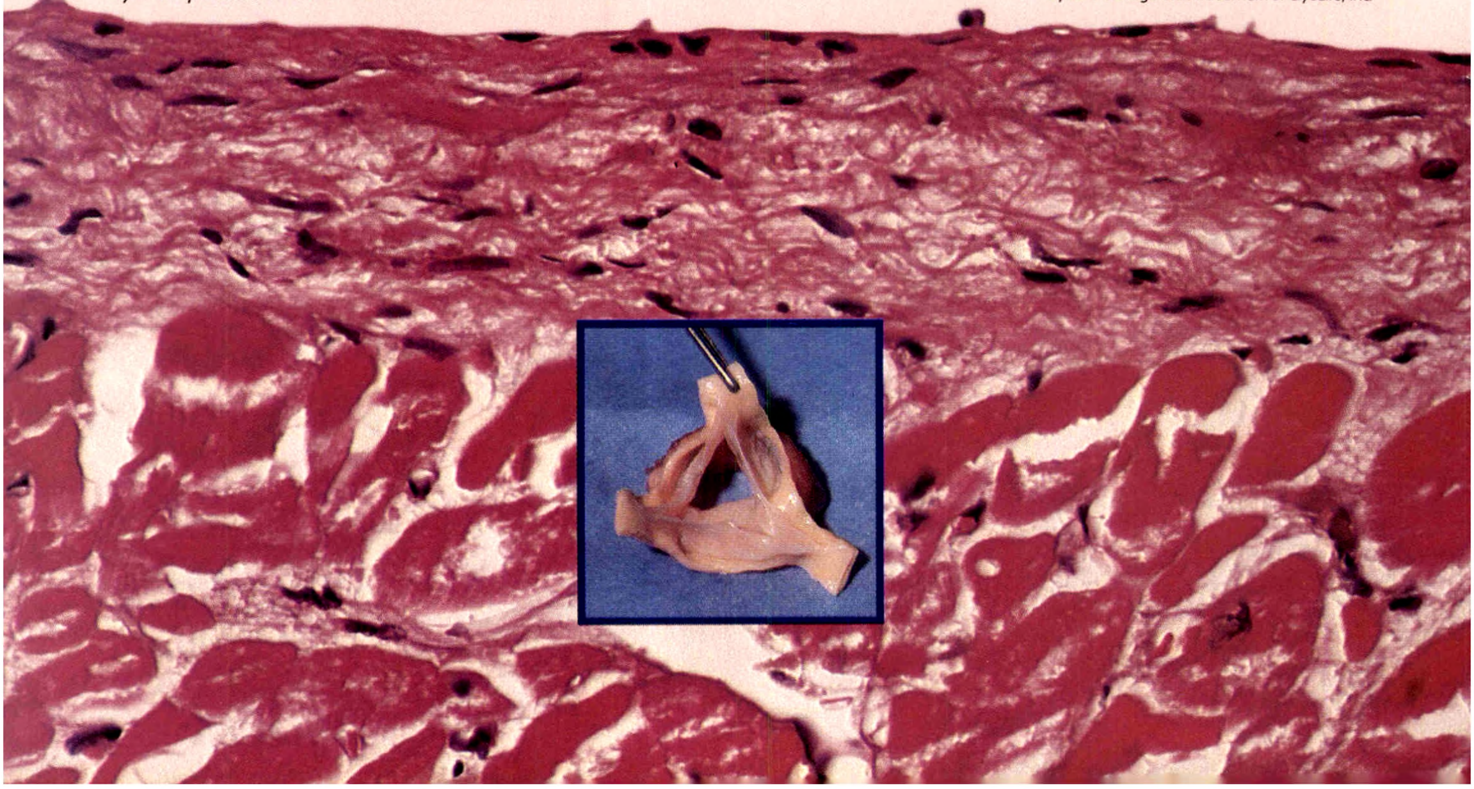

Coronary Artery Bypass Grafting for Unstable Angina Pectoris: Risk Analysis

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Unstable angina pectoris is a broad, nonspecific diagnosis encompassing a wide variety of clinical syndromes. The intravenous administration of nitroglycerin preoperatively is indicative of a more acute clinical situation, and allows for selection and analysis of a more homogeneous patient population. We reviewed the results of coronary artery bypass grafting for unstable angina defined as angina necessitating intravenous administration of nitroglycerin preoperatively. There were 129 patients (83 men and 46 women) with a mean age of 63.2 years (range, 36 to 86 years). Complications included operative death in 6.2%, postoperative low cardiac output in 11%, and perioperative myocardial infarction in 9%. Twenty perioperative variables were analyzed to identify risk factors for these end points. For operative death, age ($p < 0.05$), cross-clamp time ($p < 0.05$), and cardiopulmonary bypass time ($p < 0.001$) were significant in the univariate analysis, but only age ($p < 0.05$, $F = 4.6$) was an independent predictor using multivariate analysis (stepwise linear regression). For low cardiac output, univariate analysis demonstrated that cross-clamp time ($p < 0.01$), preoperative use of an intraaortic balloon for angina ($p < 0.05$), left ventricular score ($p < 0.05$), number of diseased coronary vessels ($p < 0.05$), and cardiopulmonary bypass time ($p < 0.001$) were significant variables. However, only use of an intraaortic balloon for angina ($p < 0.0001$, $F = 14.3$) and left ventricular score ($p < 0.005$, $F = 11.1$) were significant independent predictors in the multivariate model. For perioperative myocardial infarction, only diabetes requiring insulin ($p < 0.005$) was a significant predictor.

(Ann Thorac Surg 1989;47:569–74)

Although unstable angina pectoris is a well-recognized indication for coronary artery bypass grafting (CABG), the definition of unstable angina varies from one report to another. As a result of this inconsistency, the incidence of morbidity and mortality varies widely from one report to another, and the risk factors associated with CABG in this setting have not been well defined.

The purpose of this study is to review the results of CABG in a rigidly defined subset of patients with unstable angina and to perform an analysis of risk factors for morbidity and mortality.

Material and Methods

Between January 1, 1985, and December 31, 1987, 1,829 patients underwent isolated CABG at St. Louis University Hospital and St. Mary's Health Center. The records of these patients were reviewed to identify those patients with preinfarction unstable angina defined as angina necessitating the intravenous administration of nitroglycerin or heparin sodium, or both, at the time of surgical revascularization. Inclusion in the study required the institution of intravenous nitroglycerin with or without heparin for the treatment of severe progressive angina refractory to standard oral treatment regimens. Before revascularization, at least two electrocardiograms (ECGs) and at least one determination of the level of the myocardial-specific isoenzyme of creatine kinase were done. Patients with an evolving myocardial infarction (MI) (defined as elevation of the myocardial-specific isoenzyme of creatine kinase or new Q wave on the ECG) were excluded. Also excluded from consideration were patients with ongoing ischemia in whom percutaneous transluminal coronary angioplasty failed, those with angina after an MI (within 30 days of infarction), and those with cardiogenic shock or hemodynamic instability (defined as use of inotropic support or a documented cardiac index of <2.0 L/min/m^2 in the preoperative period).

There were 129 patients (7.1% of the total) who met these criteria. The following data were tabulated from the records of these patients: age, sex, and presence of concomitant medical problems including hypertension, cerebrovascular disease (defined as presence of transient ischemic attacks, history of stroke, and carotid endarterectomy), peripheral vascular disease (defined as presence of claudications, rest pain, or prior vascular procedure), renal dysfunction (defined as creatinine level ≥2.0 mg/dL), insulin-dependent diabetes mellitus, and chronic obstructive pulmonary disease (defined as use of bronchodilators). Also recorded were history of prior MI (>30 days previously) or prior CABG. In addition, the preoperative necessity for intraaortic balloon (IAB) counterpulsation for treatment of angina was noted.

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Catheterization findings recorded included number of diseased vessels (≥70% obstruction of luminal diameter in any plane on coronary angiography), presence of left main trunk disease (≥50% obstruction), left ventricular (LV) function as quantitated by LV score (abnormal segmental wall motion scoring system used by the Coronary Artery Surgery Study [1]), LV end-diastolic pressure, and presence of mitral regurgitation on left ventriculography.

Operative variables noted included number of distal anastomoses performed, total cross-clamp time, total cardiopulmonary bypass time, and interval (in days) from the time intravenous administration of nitroglycerin or heparin was begun until the time of CABG.

The conduct of all operations was similar. The operations were performed jointly by university faculty and surgical residents. Distal anastomoses were established under a single period of aortic occlusion. Moderate systemic hypothermia (28°C), topical iced Ringer's lactate, and cold blood cardioplegia (4°C) were employed for myocardial preservation. Supplemental doses of cardioplegia were delivered into the ascending aorta approximately every 20 minutes during the period of global ischemia. Proximal anastomoses were established during systemic warming after removal of the aortic cross-clamp; LV venting was not routinely employed.

Operative death was defined as any death during hospitalization or any death within 30 days of CABG. Also recorded were the incidence of perioperative MI (defined as a new Q wave on the ECG or elevation of the myocardial-specific isoenzyme of creatine kinase to ≥50 IU) and postoperative low cardiac output (LCO) (defined as >5 μg/kg/min of inotropic support or IAB support for >24 hours after bypass). The incidence of stroke, renal failure requiring dialysis, reoperation for bleeding, sternal wound infection or dehiscence, ventricular arrhythmias requiring medication, atrial arrhythmias requiring medication, and respiratory complications (defined as pneumonia, need for reintubation, or prolonged intubation [>48 hours after CABG]) were also noted.

Data were analyzed using the STATVIEW 512 statistical software package (Brainpower, Inc, Calabasas, CA). The χ^2 test and Fisher's exact test were used to determine significance for discrete variables. Continuous variables were analyzed using Student's t test. A p value of less than 0.05 was considered significant; a value of greater than or equal to 0.05 but less than 0.10 was considered marginally significant. All variables that were significant or marginally significant were entered into a stepwise linear regression model for multivariate analysis. Variables that were not available in at least 95% of the patients (eg, LV end-diastolic pressure, LV ejection fraction) were omitted from analysis to avoid loss of statistical power. In addition, cardiopulmonary bypass time was deleted from the multivariate analysis because it correlated strongly with cross-clamp time ($p < 0.0001$) and, in some patients, was highly skewed toward the upper ranges. In these patients, long cardiopulmonary bypass time was more likely the result of intraoperative problems than an accurate predictor of complications.

Table 1. Clinical Profile of Patients With Unstable Angina[a]

Variable	Range	Mean ± Standard Deviation	No. of Patients (%)
Continuous			
Age (yr)	36–86	63.2 ± 10.6	. . .
Left ventricular score (n = 124)	5–18	7.7 ± 3.0	. . .
LVEDP (n = 114)	2–44	17.9 ± 8.9	. . .
No. of diseased vessels	1–3	2.5 ± 0.7	. . .
Interval[b]	1–6	1.7 ± 1.2	. . .
No. of grafts	1–7	3.3 ± 1.1	. . .
Total CPB time (min)	33–274	114.5 ± 38.9	. . .
Total cross-clamp time (min)	10–133	62.3 ± 23.7	. . .
Discrete			
Male sex	. . .	. . .	83 (64.3)
Essential hypertension	. . .	. . .	81 (62.8)
Cerebrovascular disease	. . .	. . .	18 (14.0)
Peripheral vascular disease	. . .	. . .	17 (13.2)
Renal dysfunction	. . .	. . .	5 (3.9)
Insulin-dependent diabetes mellitus	. . .	. . .	7 (5.4)
Chronic lung disease	. . .	. . .	15 (11.6)
Prior MI	. . .	. . .	49 (38.0)
Prior CABG	. . .	. . .	4 (3.1)
Preop IAB support	. . .	. . .	12 (9.3)
Mitral regurgitation	. . .	. . .	13 (10.1)
Left main disease	. . .	. . .	34 (26.4)

[a] Number of patients is 129 except as noted. [b] This is the number of days from the administration of nitroglycerin to CABG.

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; IAB = intraaortic balloon; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction.

Results

The clinical profile of the patient series is depicted in Table 1. More than one third of the patient population were women (36%), and more than one fourth were 70 years of age or older (29%). Coronary angiography demonstrated triple-vessel, double-vessel, and single-vessel disease in 57%, 33%, and 10% of the patients, respectively. About 1 of every 4 patients had left main trunk stenosis. Catheterization revealed that 23% (29) of the patients had moderate to severe LV dysfunction (LV score ≥10), 41% (53) had an LV end-diastolic pressure of 20 mm Hg or higher, and 10% had angiographic evidence of mitral regurgitation. Coronary artery bypass grafting was undertaken within 24 hours of the institution of intravenous heparin or nitroglycerin in 61% (78) of the patients. The mean number of distal anastomoses per patient was 3.3.

Eight patients died, an operative mortality of 6.2%. Five of these deaths were cardiac related. One patient died of refractory arrhythmia on the first postoperative day, and

Table 2. Results of Univariate and Multivariate Analyses[a]

Variable	Groups		Univariate p Value	Multivariate	
				F	P Value
OPERATIVE DEATH (n = 127):	Survivors	Nonsurvivors			
Age (yr)	62.7 ± 10.7	71.0 ± 5.4	<0.05	4.60	<0.05
Cross-clamp time (min)	61.2 ± 23.3	79.2 ± 24.3	<0.05	3.14	NS
CPB time (min)	111.5 ± 35.5	158.4 ± 59.8	<0.001	Not included	
LOW CARDIAC OUTPUT (n = 122):	Absent	Present			
Cross-clamp time (min)	60.4 ± 22.2	78.0 ± 28.0	<0.01	3.20	NS
IAB support	7% (8/115)	29% (4/14)	<0.05	14.29	0.0001
Left ventricular score	7.5 ± 2.7	9.4 ± 4.3	<0.05	11.12	<0.0005
No. of diseased vessels	2.4 ± 0.7	2.9 ± 0.4	<0.05	1.54	NS
Age (yr)	62.8 ± 10.6	67.6 ± 9.8	<0.10	0.18	NS
CPB time (min)	109.4 ± 33.6	156.1 ± 49.0	<0.0001	Not included	
PERIOPERATIVE INFARCTION (n = 129):	Absent	Present			
Diabetes	3% (4/116)	25% (3/12)	<0.05	10.4	<0.005

[a] Where applicable, data are shown as the mean ± the standard deviation.

CPB = cardiopulmonary bypass; IAB = intraaortic balloon; NS = not significant.

4 patients died of complications of LCO at one, five, seven, and 24 days postoperatively. The 3 remaining deaths were noncardiac in cause. Two 75-year-old women died of respiratory complications following a stroke, and 1 patient died of an autopsy-confirmed pulmonary embolism on day 13.

Complications included perioperative MI in 12 patients (9.3%), postoperative LCO in 14 (11%), stroke in 4 (3.1%, includes the 2 operative deaths), renal failure in 1 (0.8%), postoperative bleeding in 5 (3.9%), sternal problems in 5 (3.9%), ventricular arrhythmias in 26 (20.2%), atrial arrhythmias in 37 (28.7%), and respiratory complications in 21 (16.3%).

Operative Death

When death was considered as the end point, only age ($p < 0.05$), cross-clamp time ($p < 0.05$), and total cardiopulmonary bypass time ($p < 0.001$) were noted to be significantly different when survivors were compared with nonsurvivors in the univariate analysis (Table 2). No marginally significant variables were noted. When the multivariate analysis was performed, only age proved to be an independent predictor of death ($p < 0.05$, $F = 4.60$).

Low Cardiac Output

In the univariate analysis, significant differences found to be related to postoperative LCO were increased total cross-clamp time ($p < 0.01$), increased cardiopulmonary bypass time ($p < 0.0001$), preoperative IAB requirement for control of angina ($p < 0.05$), increased LV score ($p < 0.05$), and number of diseased coronary vessels ($p < 0.05$). Age was found to be marginally significant ($p < 0.10$). In the multivariate analysis, only preoperative need for IAB counterpulsation ($p < 0.0001$, $F = 14.29$) and LV score ($p < 0.005$, $F = 11.12$) were found to be significant independent predictors of LCO.

Perioperative Myocardial Infarction

Of the 20 preoperative and operative variables, only insulin-dependent diabetes mellitus was found to be a significant predictor of perioperative MI. Of those patients who sustained an MI, 25% were diabetic, whereas only 3% of those who did not have an MI were diabetic. Simple regression analysis yielded a p value of less than 0.005 with an F value of 10.4.

Comment

Since the inception of CABG, there has been a continual effort to define those patients with coronary artery disease who would benefit from interventional rather than noninterventional therapy. Patients have been grouped and subclassified by symptoms and clinical situations in an attempt to produce homogeneous patient cohorts so that the natural course of the disease could be observed and the effects of intervention accurately assessed.

Originally, angina was classified by its clinical presentation; two symptom complexes, stable and unstable angina, were identified. The latter syndrome of accelerated symptoms of angina was recognized as placing the patient at a high risk for subsequent fatal and nonfatal ischemic events [2, 3]. A recent report [4] has confirmed that the tempo of angina is a significant predictor of a morbid outcome. Therefore, patients with unstable angina are logical candidates for interventional therapy.

However, the definition of unstable angina has been fairly broad and nonspecific. It has included new-onset angina, change in the clinical pattern of chronic stable angina, and any angina provoked by less than the usual stimuli. Other espoused criteria include admission to a coronary care unit to rule out MI, associated electrocardiographic changes with angina, or recurrent angina soon (<30 days) after MI [5–11]. These broad criteria have resulted in a large heterogeneous group of patients with unstable angina from which it is difficult to draw significant conclusions. The intention of this study was to identify and use strict clinical criteria for unstable angina to produce a more homogeneous patient population from which valid prognostic and therapeutic information might be drawn.

Chronic stable angina correlates closely with critical fixed stenosis of coronary arteries or reversible coronary spasm. Exertion or emotional upset results in increased myocardial oxygen consumption, which cannot be adequately compensated by increased coronary flow because of the fixed arterial obstruction or spasm. Other factors affecting this process include the availability of collateral circulation and the use of standard oral antianginal medication such as β-blockers, calcium-channel blockers, and vasodilators.

Unstable angina appears to be due to a different underlying process. Anatomical [12, 13], angiographic [14, 15], and angioscopic [16, 17] studies have shown that unstable angina is pathophysiologically similar to the intracoronary events that occur with MI. In both syndromes, platelet thrombus formation has been noted, usually superimposed on either arterial spasm or rupture of an ulcerated atherosclerotic plaque. In this setting, myocardial ischemia can occur as a result of either subtotal occlusion of the vascular lumen or thrombus fragmentation with distal embolization. Davies and Thomas [12] and Falk [13] have suggested that the subsequent behavior of such a thrombus determines the clinical outcome. Thrombus dissolution can result in an episode of unstable angina only, but thrombus progression with prolonged vascular occlusion can result in MI. The situation appears analogous to that of crescendo transient ischemic attacks, which may or may not culminate in a frank stroke.

Patients with unstable angina are usually treated aggressively with antianginal therapy in the setting of an intensive care unit while the diagnosis of MI is excluded. Those who become asymptomatic with such treatment can then undergo revascularization with an operative mortality virtually identical to that of patients having elective CABG [6, 11]. On the other hand, those who are refractory to such measures are then usually treated with intravenous nitroglycerin or heparin, or both. It is these patients, unresponsive to oral therapy and without enzymatic evidence of myocardial injury, who comprise the patient group with what we have called unstable angina. These criteria define a cohort of patients with unstable angina who are at high risk for subsequent infarction and death. We believe this is a relatively homogeneous population from which valid prognostic and therapeutic information can be drawn, thus allowing for more accurate comparison of patients and results between institutions.

The operative mortality in this series (6.2%) is higher than that of elective revascularization (<2% at most institutions). Risk factor analysis of the clinical characteristics of the patient population help in understanding this difference. It has been shown that the independent predictors of operative mortality in CABG are urgency of surgical revascularization, advanced age, female sex, congestive heart failure, and incomplete revascularization, with urgent operation being the most powerful predictor [18]. By definition, patients in our study fall into the "high-risk" category, as all underwent urgent revascularization. The relatively high mean age and the high proportion of women also help to explain the elevated operative mortality. Multivariate analysis of the known predictors of outcome for CABG demonstrated that only age was significant in the present series, perhaps because of the relatively small patient population that results from the strict selection criteria.

Table 3. Operative Outcome in Recent Studies

Reference	Year	Operative Mortality (%)	Low Cardiac Output (%)	Perioperative Infarction (%)
Jones et al [7]	1982	1.2	12	3.8
Rankin et al [11]	1984	4.2	9	6.3
Eugene et al [8]	1985	3.9	. . .	11.1
Christakis et al [10]	1986	2.8	18	8.6
Teoh et al [6]	1987	8.5	21	11.2
Luchi et al [9]	1987	4.1	. . .	. . .
Naunheim et al [present series]	1989	6.2	11	9.3

The operative mortality is also 2% to 3% higher than in many other series dealing with CABG for unstable angina (Table 3) [6–11]. This should be examined with an eye toward risk stratification. The highest operative mortality among patients with unstable angina undergoing CABG recently reported is 8.5% [6]. However, nearly 42% of the 224 patients in that series requiring urgent revascularization not only had angina refractory to intravenous nitroglycerin but also an MI without a new Q wave. When those patients with documented MI were excluded from analysis, the operative mortality was 6.1%, a figure virtually identical to our own. In contrast, Jones and associates [7] reported a 1.2% operative mortality among 72 patients. However, compared with the present report, their series appears to consist of a different patient population: a lower mean age (57 years versus 63 years), fewer women (25% versus 36%), and a lower incidence of left main stenosis (9% versus 26%) and triple-vessel disease (26% versus 57%) (Table 4). In addition, it is difficult to determine how many of the CABG procedures were undertaken urgently, as only 36% of those patients required intravenous nitroglycerin.

Similar differences in clinical profile can be seen in the reports of Eugene [8], Luchi [9], and their associates. Both of these series comprised younger patients (mean age, 58 and 56 years, respectively), and neither included women. In addition, Luchi and colleagues [9] had no patients with left main disease or severe LV dysfunction, and less than 50% of their patients had triple-vessel disease. Both series had operative mortalities of approximately 4%.

The incidence of perioperative MI was 9.3% in our series, which is similar to that in other reports published in the 1980s (see Table 3). Although earnest efforts have been made to detect ongoing myocardial necrosis pre-

Table 4. Clinical Profile in Recent Studies

Reference	Year	No. of Patients	Mean Age (yr)	Female Sex (%)	Left Main Trunk Disease (%)	Triple-Vessel Disease (%)
Jones et al [7]	1982	78	57	25	9	26
Rankin et al [11]	1984	48	57	19	16	58
Eugene et al [8]	1985	207	58	0	35	67
Christakis et al [10]	1986	140	61	22	20	72
Teoh et al [6]	1987	224	60	26	17	59
Luchi et al [9]	1987	231	56	0	0	45
Naunheim et al [present series]	1989	129	63	36	26	57

operatively, it is possible that some of these patients actually had an undetected subendocardial MI before revascularization. Previous authors have suggested that perioperative MI is associated with urgency of operation [6], LV function [5], pain unresponsive to medical therapy, and type of myocardial protection [10]. No one factor has been consistently reported as a risk factor for perioperative MI; therefore it is difficult to come to any certain conclusion. Three (43%) of the 7 patients in our series with insulin-dependent diabetes mellitus sustained a perioperative infarction. Our finding of insulin-dependent diabetes mellitus as a risk factor has not been noted in prior reports and also must be considered tentative.

Postoperative LCO occurred in 11% of our patients, an incidence that is in concert with other reports (see Table 3). The only independent predictors of this complication were poor LV function and necessity for IAB support in the treatment of angina during the preoperative period. Patients requiring preoperative IAB support had a one in three chance (4/12) of sustaining LCO. Other authors [6, 10] have also reported LV dysfunction as a risk factor, and have further suggested that preoperative persistent electrocardiographic changes with chest pain and the method of myocardial protection during operation may also be predictors of postoperative LCO. Because blood cardioplegia has been routinely used at our institution since 1977, we have not evaluated type of cardioplegia as a risk factor [19]. Although the type of cardioplegia has not been proved to be a risk factor during elective cardiac procedures [20, 21], blood cardioplegia has been demonstrated to result in lower rates of perioperative MI and postoperative LCO in those patients with prolonged periods of global ischemia [22] and in those undergoing urgent revascularization for unstable angina [10]. Further modification of techniques of myocardial preservation during global ischemia are currently being investigated. These include energy substrate repletion with enriched cardioplegic solution [23], retrograde coronary sinus perfusion [24, 25], and the use of free oxygen radical scavengers in the perfusate solution [26, 27]. These refinements may hold the promise of improved myocardial preservation with an attendant reduction in perioperative morbidity and mortality.

The appropriate management of unstable angina continues to be controversial. With the advent of and improvements in thrombolysis and percutaneous transluminal coronary angioplasty, these techniques are now being used frequently in the treatment of acute unstable angina instead of CABG. It is likely that optimal treatment for unstable angina will require percutaneous transluminal coronary angioplasty (with or without thrombolysis) and CABG to be used in a complementary, noncompetitive fashion. As future studies to examine the appropriate role of these interventional methods will undoubtedly be undertaken, it is critical that the definition of unstable angina be refined. Only then can one be assured that similar groups of patients will be compared in valid fashion. The necessity for preoperative intravenous nitroglycerin or heparin, or both, is a reproducible and objective criterion that can be used to define a specific group of patients with unstable angina pectoris. Furthermore, there is accumulating evidence that the pathological changes associated with this entity result from morphological and coagulation abnormalities specifically susceptible to this type of preinterventional therapy.

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Deleterious Effects of Shock in Internal Mammary Artery Anastomoses

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Internal mammary arteries (IMAs) are increasingly used for coronary artery revascularization. However, spastic reactions after IMA–coronary artery anastomoses have been reported. Internal mammary artery flow and the effects of sudden hypovolemia, gradual hypovolemia, papaverine hydrochloride, nitrates, and epinephrine were evaluated in a canine model (n = 10) (body weight, 19 ± 5 kg) without interference from coronary artery resistance by dissecting the IMA as a pedicle, calibrating the flowmeter during free IMA flow, and anastomosing the IMA to the right atrium. Sudden hypovolemia (withdrawal of 20% of circulating blood volume over 90 seconds) caused significant modifications ($p < 0.01$) of the following hemodynamic variables: heart rate (+12%), right atrial pressure (−17%), pulmonary artery pressure (−20%), wedge pressure (−30%), aortic pressure (−49%), cardiac output (−33%), distal IMA pressure (−54%), and IMA flow (−85%). During hypovolemia, IMA flow could not be increased with topical application of papaverine, but baseline values were achieved after retransfusion of the withdrawn blood volume. Gradual hypovolemia and application of large doses of nitrates showed less dramatic effects, and injection of an epinephrine bolus under normovolemic conditions increased aortic pressure and IMA flow. Under sever hypovolemia, however, administration of an epinephrine bolus provoked only a minimal increase in aortic pressure and a contrasting decrease in IMA flow. We conclude that sudden, severe hypovolemia can lead to disproportionate IMA flow reduction and that pharmacological interventions are delicate under these circumstances.

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The internal mammary artery (IMA) was introduced for direct coronary artery revascularization in 1965 [1] and is increasingly used nowadays because of its better long-term patency [2–6]. The superior long-term patency rates are reflected in an improved long-term survival and a decreased rate of reoperation [7, 8]. However, initially the IMA graft delivers less flow to the coronary arteries in comparison with saphenous vein grafts [9], and this lower flow can be reduced even more because of spastic reactions of the IMA [10]. The present study was designed to evaluate IMA flow isolated from the coronary arterial bed as a function of different hemodynamic situations that can occur after coronary artery bypass grafting (eg, severe bleeding, arrhythmia, and low output) and as a function of various pharmacological interventions.

Material and Methods

The study included 10 mongrel dogs with a body weight of 19 ± 5 kg (mean ± standard deviation). All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

General anesthesia was induced with Pentothal (thiopental sodium) and maintained with volatile anesthetics. After a median sternal splitting incision, the right IMA was taken down with a muscular pedicle by combined low-power cautery and ligation. Then the pericardium was opened and the right atrium exposed.

Continuous recording of the electrocardiogram (heart rate), central venous pressure, pulmonary artery pressure and wedge pressure, and arterial pressure was performed with a seven-channel Gould recording system. Cardiac output was assessed by thermodilution (Edwards) at regular intervals. An electromagnetic flow probe (Biotronex, Kensington, MD) was placed at the origin of the IMA. After measurement of free IMA flow (volumetric tank) and calibration of the flowmeter (Biotronex), the distal end of the IMA was implanted in the right atrial appendage end to side with a 7-0 monofilament polypropylene continuous suture and 24-gauge catheter with a pressure-measuring line connected to a Statham transducer was installed at the junction between the middle and distal third of the IMA. This model—the IMA dissected free as a pedicle and implanted in the right atrium—allows study of the effects of various conditions on the isolated IMA independent from the coronary arterial bed.

Hemodynamic Studies

The hemodynamic variables already mentioned as well as IMA flow and distal IMA pressure were analyzed under the following conditions: normovolemia and steady state; sudden hypovolemia (withdrawal of 20% of calculated circulating blood volume over 90 seconds); gradual hypovolemia (withdrawal of 20% of calculated circulating

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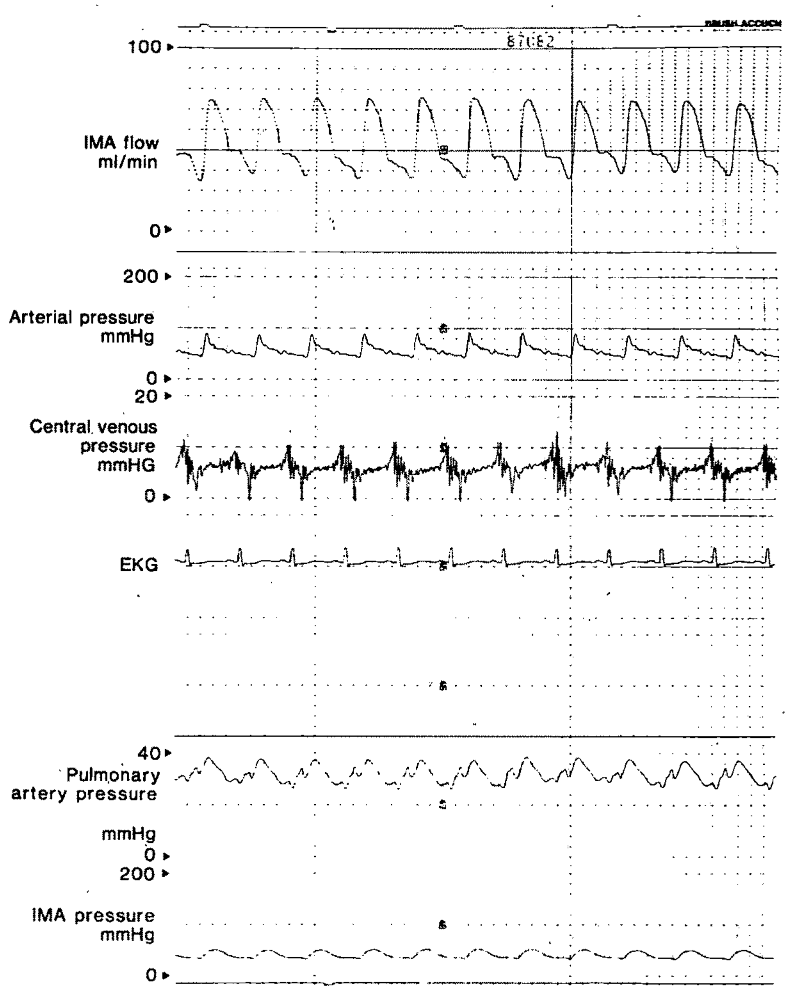

Fig 1. Continuous registration (pulsatile model) of hemodynamics in general (electrocardiogram [EKG], central venous pressure, pulmonary artery pressure, and arterial pressure) and hemodynamics of the internal mammary artery (IMA) (distal pressure and flow). Paper speed is 25 mm/s.

blood volume over 240 seconds); bolus of nitrates (Perlinganit [glyceroltrinitrate; Schwartz, Liestal, Switzerland], 500 μg/kg); bolus of epinephrine (5 μg/kg); and sudden hypovolemia and bolus of epinephrine (5 μg/kg). Data on the monitored variables were recorded continuously and read every 60 seconds before, during, and after the interventions until stabilization of the hemodynamic variables occurred. After the administration of each agent, sufficient time was allowed for restitution of the preadministration hemodynamic values. Hypovolemia was corrected by retransfusion of the withdrawn volume.

Data Analyses

Quantitative data are presented in the tables as the mean ± the standard deviation. Comparison of quantitative data was made using Student's t test for paired variables where appropriate. Statistical significance was confirmed by a p value of less than 0.05.

Results

Continuous registration (pulsatile mode) of IMA flow, arterial pressure, central venous pressure, electrocardiogram, pulmonary artery pressure, and distal IMA pressure is shown in Figure 1. The synchronous pulses of arterial pressure and IMA pressure and the consecutive pulsatile IMA flow are documented. Figure 2 shows continuous registration of the hemodynamic variables (mean mode) during fast withdrawal of 20% of the calculated circulating blood volume (sudden hypovolemia, 90 seconds), stabilization, and retransfusion (240 seconds) of the same blood volume. During hypovolemia, IMA flow dropped to almost 0 mL/min, and arterial pressure, measured in the aorta, fell to about 50% as did the pressure in the distal IMA. There was a slight recovery of all curves during stabilization and progressive recovery during retransfusion of the withdrawn volume. After retransfusion, all recorded variables nearly reached the preshock values.

The results of serial studies in 10 animals with hypovolemic shock are given in Table 1. For a mean reduction of cardiac output from 3.3 to 2.2 L/min (−33%), aortic pressure fell from 94 to 48 mm Hg (−49%), distal IMA pressure decreased from 71 mm Hg to 33 mm Hg (−54%), and IMA flow dropped from 66 mL/min to 10 mL/min (−85%). The differences measured before and after withdrawal of the predetermined volume are highly significant for all variables (see Table 1). The reduced IMA flow under hypovolemic conditions could not be increased by topical application of papaverine hydrochloride.

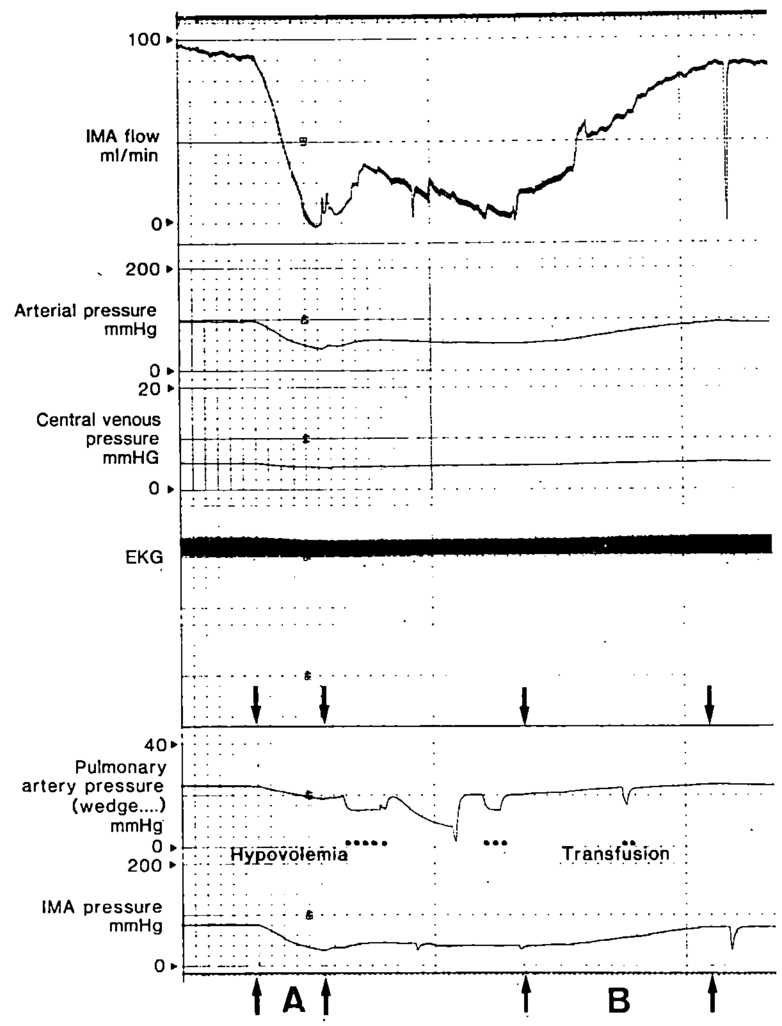

Fig 2. Continuous registration (mean mode) of hemodynamics during sudden hypovolemia (A, 90 seconds), stabilization (between A and B), and retransfusion (B). Mechanical zero of internal mammary artery (IMA) flowprobe is checked twice during stabilization and once at the end of retransfusion (no modification). Wedge pressure is measured at the end of hypovolemia, at the end of stabilization, and during retransfusion. Paper speed is 1 mm/s.

Table 1. Measurements During Sudden Hypovolemia[a]

Variable	Baseline	Shock	Percent Change	p Value
Heart rate (beats/min)	138 ± 20	154 ± 20	+12	<0.01
Right atrial pressure (mm Hg)	7 ± 2	6 ± 2	−17	<0.01
Pulmonary artery pressure (mm Hg)	15 ± 6	12 ± 5	−20	<0.001
Wedge pressure (mm Hg)	10 ± 5	7 ± 3	−30	<0.001
Aortic pressure (mm Hg)	94 ± 22	48 ± 4	−49	<0.001
Cardiac output (L/min)	3.3 ± 0.8	2.2 ± 0.9	−33	<0.001
Distal IMA pressure (mm Hg)	71 ± 20	33 ± 9	−54	<0.001
IMA flow (mL/min)	66 ± 30	10 ± 9	−85	<0.001

[a] Measurements were performed 120 seconds after onset of withdrawal of volume or 30 seconds after completed withdrawal of volume (20% calculated circulating blood volume over 90 seconds). Values are given as mean ± the standard deviation where appropriate.

IMA = internal mammary artery.

The values of the other analyzed conditions are given in Table 2. Gradual hypovolemia (withdrawal of the same amount of blood as in hypovolemic shock but over a longer period, 240 seconds) showed less dramatic effects. During the observation period, aortic pressure dropped from 85 to 55 mm Hg (−35%), and IMA flow dropped from 71 mL/min to 34 mL/min (−51%).

Similar effects were observed after the administration of high doses of nitrates as a bolus. For an aortic pressure drop from 94 to 49 mm Hg (−48%), IMA flow decreased from 117 to 34 mL/min (−71%).

Injection of an epinephrine bolus under normovolemic conditions provoked a slight increase of aortic pressure from 70 to 85 mm Hg (+21%) and also an increase of IMA flow from 88 to 138 mL/min (+57%). Under severe shock, however, the administration of an epinephrine bolus provoked only a minimal increase of aortic pressure from 45 to 48 mm Hg (+7%) and a contrasting decrease of IMA flow from 30 to 18 mL/min (−40%).

Comment

Sudden severe hypovolemia led to a disproportionate reduction in IMA flow in the canine model, as documented in Figure 2 and demonstrated in serial analyses (n

Table 2. Measurements Under Other Conditions[a]

Condition	Interval (s)	Aortic Pressure (mm Hg)	IMA Pressure (mm Hg)	IMA Flow (mL/min)
Normovolemia to gradual hypovolemia[b]	0	85 ± 15	67 ± 17	71 ± 16
	120	60 ± 6	45 ± 11	50 ± 21
	240	55 ± 14	39 ± 14	34 ± 16
Normovolemia + nitrates bolus (500 μg/kg)[c]	0	94 ± 10	76 ± 12	117 ± 60
	60	49 ± 7	30 ± 7	34 ± 10
Normovolemia + epinephrine bolus (5 μg/kg)	0	70 ± 5	58 ± 8	88 ± 13
	60	85 ± 5	70 ± 10	138 ± 13
Severe hypovolemia + epinephrine bolus (5 μg/kg)	0	45 ± 5	30 ± 5	30 ± 20
	60	48 ± 7	34 ± 4	18 ± 12

[a] Values are given as the mean ± the standard deviation. [b] Gradual hypovolemia was achieved by withdrawal of 20% of calculated circulating blood volume over 240 seconds. [c] Perlinganit was given.

IMA = internal mammary artery.

= 10) in Table 1, where the change in IMA flow was −85% as a function of a −49% change in aortic pressure. The pressure difference between the two ends of the IMA (aortic pressure − central venous pressure) was 87 mm Hg before hypovolemia and 42 mm Hg after hypovolemia (change in pressure of 52%). Therefore, the drop in IMA flow was also disproportionate in comparison with the pressure difference before and after hypovolemia. This reaction can be explained by the stress-induced α-adrenergic sympathetic stimulation, ie, release of norepinephrine, and triggering of other vasoactive mediators, thereby provoking peripheral vasoconstriction. It has been shown that the IMA is a living conduit [11] that will react to vasoconstriction after α-adrenergic stimulation.

Disproportionate flow reduction in the IMA used as the graft for coronary artery revascularization can have deleterious effects in critical situations (eg, weaning from cardiopulmonary bypass [10]) and especially in patients with few collaterals (eg, after resection of coronary artery aneurysms [12]).

After retransfusion and stabilization, gradual hypovolemia provoked by withdrawal of the same amount of blood over a period of 240 seconds instead of 90 seconds showed less dramatic effects with a change in aortic pressure of −35% and a nearly proportionate reduction in IMA flow (51%). The difference observed between sudden hypovolemia and progressive hypovolemia can be explained by the lack of time for adequate autoregulation in the former situation.

A massive bolus injection of nitrates led to a reaction similar to that with gradual hypovolemia: the change in aortic pressure of −48% is in the same range as the change in IMA flow (−71%). It can be speculated that the relatively proportionate decreases are due to the vasodilating effects of the nitrates, the relatively gentle secondary onset of hypovolemia, or both.

An epinephrine bolus under normovolemic conditions caused a significant increase in IMA flow (+57%, $p < 0.05$). This effect is due to the positive chronotropic and positive inotropic effects of high doses of epinephrine and the consecutive increased cardiac output. Increased IMA flow under normovolemic conditions has been previously documented in other studies in which the IMAs were implanted in the coronary arteries [13, 14]. However, those situations did not permit separation of the vasomotor changes in the coronary vascular bed from those in the IMAs. The two vascular beds represent serial resistors and should be studied independently to determine the relative contribution of each segment to the observed changes in IMA flow.

The administration of an epinephrine bolus after sudden hypovolemia provoked, as expected, some increase of aortic pressure (+7%). However, when shock is very severe and epinephrine doses are high enough, the slight increase of aortic pressure appears mainly to be due to extreme vasoconstriction, as documented by a decrease of IMA flow (−40%). This situation might be difficult to overcome if coronary artery blood flow is predominantly supplied by the IMAs. We are aware of the fact that these analyses were performed with extreme volume shifts and high doses of vasoactive drugs. In this study, however, we were dealing with a healthy myocardium in contrast to clinical practice where, when problems occur, the myocardial activity might be termed "weak action," and no or only a slight response can be expected after application of positive inotropic agents.

We conclude that sudden, severe hypovolemia can lead to a disproportionate reduction in IMA flow and that pharmacological interventions are delicate under these circumstances.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the cardiothoracic operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1991 may begin the recertification process in 1989. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1989. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Extrathoracic and Transthoracic Management of Vascular Disease of the Aortic Arch Branches: A 16-Year Experience

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To determine factors influencing results of operation for proximal brachiocephalic arterial disease, a 16-year review of 74 consecutive patients was undertaken. A total of 62 subclavian, 14 common carotid, 6 innominate, and 2 vertebral arteries were revascularized during 79 procedures. The approach was transthoracic in 12 operations and extrathoracic in 67. Mean follow-up was 57 ± 45 months. Two patients (2.5%) died of stroke after extrathoracic revascularization of the common carotid artery. Cumulative 5-year and 10-year freedom from neurological events was 81% and 75%, respectively. The best results were obtained with transthoracic procedures, with revascularization of the subclavian artery rather than the common carotid artery, and in operations performed in patients without associated distal carotid disease. In view of the recent progress in operative techniques and postoperative surgical care, the choice between the transthoracic approach and the extrathoracic approach should not be biased; rather, they should remain equal and viable alternatives based on anatomical and clinical features of the individual patients.

(Ann Thorac Surg 1989;47:580–5)

Revascularization for proximal brachiocephalic arterial disease is an uncommon procedure in comparison with the total surgical experience with carotid bifurcation. The many controversies in the surgical literature concerning the best treatment of such a lesion give this topic a special interest.

Most of the studies [1–8] covered an extended period, during which many changes have been made in operative and anesthetic techniques. Introduction of extrathoracic reconstructions as an alternative intervention to the older anatomical transthoracic approach led to the abandonment of the latter procedure, thereby generating debate. Analysis of surgical results is also difficult because of the wide patterns of arteries involved in the disease.

In seeking to define factors influencing results of operation for proximal lesions of the branches of the aortic arch, we reviewed our personal experience over an extended period of 16 years.

Material and Methods

Between January 1972 and December 1987, 74 patients underwent 79 surgical reconstructions for proximal lesions of the branches of the aortic arch on our cardiovascular service. During the 16-year period under review, 1,200 surgical revascularization operations of other extracranial vessels were performed; operations on brachiocephalic arteries therefore constitute 6.2% of our total surgical experience for cerebrovascular disease.

There were 44 women (59%) and 30 men (41%) whose age ranged from 32 to 73 years (mean age, 63 ± 10 years; median age, 63 years). Atherosclerosis was the causative factor in all but 1 patient. A 32-year-old woman was seen with clinical and pathological findings of Takayasu's arteritis. All patients had one or more manifestations of associated cardiovascular risk factors (Table 1). Aneurysmatic or occlusive disease of the aorta and lower limb arteries was associated in 32 patients (43%).

At the original preoperative surgical examination, cerebral symptoms were attributed to hemispheric ischemia in 23 patients (31%) and to vertebrobasilar insufficiency in 38 patients (51%); 7 patients (9%) had both hemispheric and nonhemispheric symptoms. Upper limb ischemia was present alone (4 patients) or in combination with cerebral symptoms (30 patients) in 46% of the patients. A total of 9 patients (12%) had experienced previous strokes (cerebrovascular accidents), and 59 patients (80%) had sustained transient ischemic neurological events (transient ischemic attacks). One patient (1%) was seen in the emergency room with a ruptured subclavian aneurysm. Only 1 patient in the series was asymptomatic (1%).

All patients underwent arch study or four-vessel arteriography. A total of 62 subclavian arteries, 6 innominate arteries, 14 common carotid arteries, and 2 vertebral arteries were revascularized. Associated major stenosis (reduction in luminal diameter >50%) of the carotid bifurcation was present in 51 patients (69%), ipsilateral in 92% and contralateral in 8%.

Surgical Management

A total of 79 procedures were performed (Table 2). They were individualized for each patient depending on period of operation, presenting symptoms, and extension of

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Table 1. Risk Factors in 74 Patients[a]

Factor	No. of Patients
Smoking	61 (82)
Cardiac disease	45 (61)
Coronary disease	32 (43)
Other[b]	13 (18)
Hypertension	43 (58)
Diabetes[c]	14 (19)
Chronic obstructive pulmonary disease	16 (22)
Renal failure	6 (8)
Alcohol abuse	11 (15)
Obesity	14 (19)
Hyperlipemia	14 (19)

[a] Numbers in parentheses are percentages. [b] This includes congestive heart failure or persistent arrhythmia. [c] This includes patients who are under medical treatment or have an abnormal glucose tolerance.

disease. Fifty percent of the 74 patients underwent simultaneous or staged carotid endarterectomy.

TRANSTHORACIC PROCEDURES. This approach was chosen in 12 patients with good respiratory functions in the presence of severe or multiple involvement of brachiocephalic arteries. Twelve operations were performed to treat 17 arterial lesions through a partial median sternotomy. Four (33%) were performed before 1980 and eight (67%), after 1980.

Seven arteries (41%) were repaired on the left side and 10 (59%) on the right side. Four patients underwent multiple reconstructive bypass operations; two involved the placement of bifurcation grafts (aorta–innominate artery–left subclavian artery bifurcation graft; aorta–left subclavian artery–left common carotid artery bifurcation graft), and two were staged procedures (aorta–right common carotid artery graft + innominate endarterectomy + axilloaxillary graft; subclavian artery–subclavian artery graft + subclavian artery–carotid artery graft).

Table 2. Types of Operation Performed During Consecutive Periods of Study

Procedure	1972–1979 No.	1972–1979 %	1980–1987 No.	1980–1987 %	Total No.
Extrathoracic					
Carotid–subclavian	22	67	17	37	39
Subclavian transposition	0	. . .	16	35	16
Axilloaxillary	1	3	2	4	3
Subclavian–subclavian	3	9	0	. . .	3
Carotid–axillary	1	3	0	. . .	1
Carotid–carotid	0	. . .	1	2	1
Vertebral–tyreocervical	1	3	0	. . .	1
Vertebral–subclavian	0	. . .	1	2	1
Thrombectomy	1	3	1	2	2
Transthoracic					
Aorta–subclavian	3	9	2	4	5
Aorta–innominate	0	. . .	1	2	1
Carotid–subclavian	0	. . .	1	2	1
Multiple reconstructions	0	. . .	4	9	4
Thrombectomy	1	3	0	. . .	1
Total	33		46		79

Eight Dacron grafts (67%) and four polytetrafluoroethylene grafts (33%) were implanted.

EXTRATHORACIC PROCEDURES. Sixty-seven extrathoracic operations were performed in 64 patients. One patient underwent bilateral reconstruction (aorta–subclavian artery–subclavian artery bifurcation graft + innominate artery–left common carotid artery graft), and 2 patients were reoperated on after failure of previous extrathoracic bypass procedures. One patient underwent extrathoracic bypass grafting on the site contralateral to a transthoracic revascularization. Of the 39 carotid–subclavian artery bypass procedures performed, 30 were utilized to control subclavian lesions and nine to control proximal carotid lesions. The vertebral artery was anastomosed in an end-to-side fashion to the cervical trunk in 1 patient and to the subclavian artery in another patient.

Direct subclavian–carotid transposition was carried out in 16 patients, and simple subclavian or common carotid endarterectomy was performed in 2. Other extraanatomical reconstructions were used extensively in 8 patients. Of 47 extrathoracic bypass grafts performed, a polytetrafluoroethylene graft was used in 26 instances (55%), a Dacron graft in ten (21%), and an autologous vein graft in 11 (23%). Autologous vein and Dacron grafts were preferred before 1978. Since then, polytetrafluoroethylene grafts have been used in the majority of extrathoracic reconstructions.

Follow-up

Operative and hemodynamic data were noted from surgical registries and hospital charts. Long-term follow-up data were obtained from hospital outpatient or office examination records, and were supplemented by correspondence or telephone interviews with the patient or referring physician.

All but 3 patients were followed from the time of operation to death or to the end of the present study period (mean follow-up, 57 ± 45 months). Three patients (4%) were lost to follow-up at 1, 2, and 4 months after extrathoracic operations; none of these patients had evidence of recurrence of symptoms or differences in blood pressure between the arms.

Statistical Analysis

The χ^2 test, Student's t test, and Fisher's exact test were used when appropriate. Early and late neurological morbidity and mortality, graft patency, and survival rate were tabulated according to the Kaplan-Meier method. Actuarial curves were compared with the log-rank test. A p value of less than 0.05 was representative of a significant difference.

Table 3. Early and Late Neurological Complications After 79 Procedures[a]

		Extrathoracic		Transthoracic	
Complication	Total	No.	%	No.	%
Operative CVA	5	5 (2)	7	0	. . .
Symptoms unchanged	5	5	7	0	. . .
Late TIA and CVA	5	4 (2)	6	1	8

[a] Numbers in parentheses are the number of fatal cerebrovascular accidents. Percentages are based on 74 patients (some patients had more than one procedure).

CVA = cerebrovascular accident; TIA = transient ischemic attack.

Table 5. Major Nonneurological Complications

	Extrathoracic		Transthoracic	
Complication	No.	%	No.	%
Horner's syndrome	3/67	4	0	. . .
Cranial nerve injury	2/67	3	0	. . .
Wound infection	2/67	3	1/12	8
Lung atelectasis	2/67	3	1/12	8

Results

Early Results

Operative mortality after 79 interventions was 2.5% (Table 3). There were 2 operative deaths after the 67 extrathoracic procedures (3%) and no deaths after the 12 transthoracic interventions. Both patients died of a fatal cerebrovascular accident after revascularization of the common carotid artery by carotid–subclavian bypass grafting. Three other operative strokes occurred after carotid–subclavian artery bypass procedures. Two of these patients had undergone revascularization of the left subclavian artery, and recovered completely; the other patient, with severe occlusion of the common carotid artery, had a persistent cerebrovascular accident with contralateral hemiparesis. Three of the 5 patients who sustained operative strokes had undergone simultaneous internal carotid endarterectomy. Five patients (7%) in the extrathoracic group did not achieve any benefit from operation and were considered to have had unsuccessful operations.

Table 4 shows operative data and length of hospital stay according to the surgical approach. A total of 9 blood units were transfused without accident in 3 patients in the transthoracic group. Nonneurological operative complications are shown in Table 5. The mean postoperative increase in systolic blood pressure was 61 ± 70 mm Hg in the transthoracic group and 44 ± 39 mm Hg in the extrathoracic group (p = not significant).

Late Results

Of 64 patients discharged without symptoms, 5 (8%) eventually sustained new neurological events during the follow-up study. Two of them died of a fatal cerebrovascular accident 32 and 64 months after extrathoracic revascularization of the subclavian artery. One patient experienced episodes of amaurosis fugax in the right eye 41 months after aorta–innominate artery bypass grafting. Three patients experienced either transient ischemic attacks (2) or a cerebrovascular accident (1) on the site contralateral to previous operation at 27, 40, and 71 months of follow-up. These patients were not considered to have had unsuccessful operations.

Eleven of the 15 patients (73%) who experienced operative or late neurological complications or who had no change in symptoms were operated on in the earliest period of the study compared with 4 (27%) who had operation after 1980. Cumulative 5-year and 10-year freedom from neurological morbidity and mortality for the entire series was 81% and 75%, respectively (Fig 1). Functional results were significantly better in the last 8 years ($p < 0.05$).

Figure 2 shows functional results by surgical approach and by type of artery revascularized. Operations performed through a transthoracic approach and those used to revascularize the subclavian rather than the common carotid artery achieved the best results, the difference being significant ($p < 0.05$). Of 51 patients with associated distal carotid artery disease, 14 (27%) were classified as having an unsuccessful operation compared with only 1 (4%) of 28 patients without evidence of carotid disease. Actuarial late functional results in patients with associated

Table 4. Operative and Hospital Data

Variable	Extrathoracic	Transthoracic	p Value[a]
Total operative time (min)	135 ± 36	200 ± 47	<0.05
Estimated operative blood loss (mL)	227 ± 214	910 ± 672	NS
Postoperative hospital stay (days)	6 ± 3	9 ± 3	NS

[a] Student's t test was used.

NS = not significant.

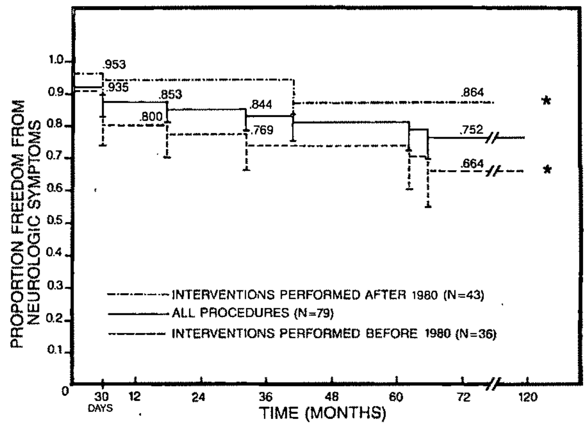

Fig 1. Actuarial freedom from neurological symptoms (Kaplan-Meier plot). Interventions performed before 1980 versus interventions performed after 1980, $p < 0.05$ *(*) (log-rank test).*

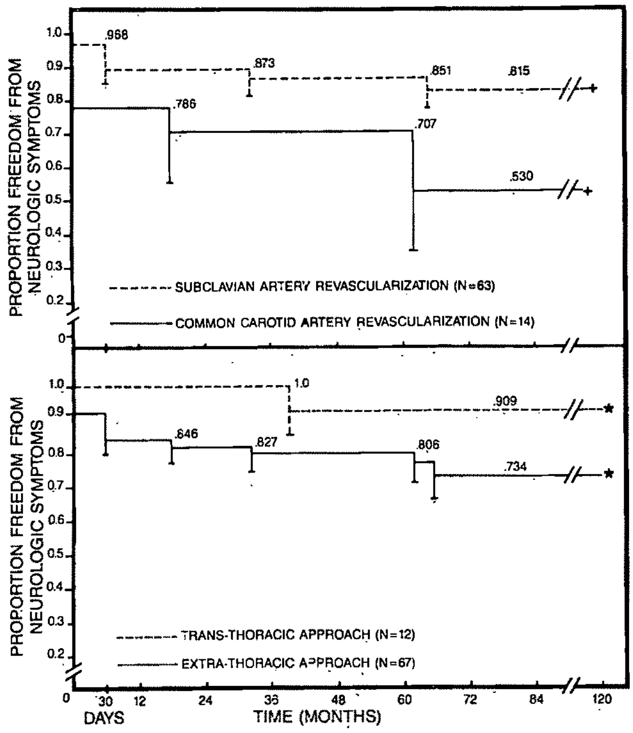

Fig 2. Actuarial freedom from neurological symptoms according to artery revascularized and operative approach (Kaplan-Meier plot). Subclavian versus common carotid artery, p < 0.05(+) and transthoracic versus extrathoracic approach, p < 0.05 (*) (log-rank test).

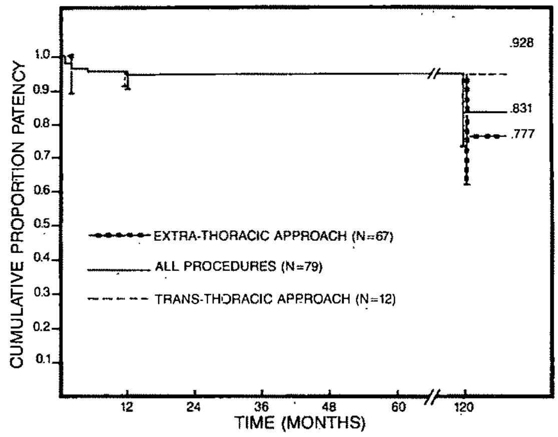

Fig 4. Actuarial patency according to operative approach (Kaplan-Meier plot). Transthoracic versus extrathoracic approach, p = not significant (log-rank test).

carotid lesions were significantly worse than in other patients ($p < 0.0001$) (Fig 3).

Graft Patency

Seven grafts became occluded during follow-up. The material used in these reconstructions was autogenous vein (two grafts), polytetrafluoroethylene (three grafts), and Dacron (two grafts). In 1 patient, failure of the graft resulted in recurrence of a preoperative transient ischemic attack. Either a thromboembolectomy with patch angioplasty or a new bypass procedure was successful in 3 patients. Actuarial 5-year and 10-year patency was 93% and 83%, respectively (Fig 4). Segregating patients by type of surgical approach, actuarial 5-year and 10-year patency after extrathoracic operations was 93% and 73%, respectively, and 93% and 93%, respectively, after transthoracic operations. The difference is not significant.

Survival

A total of 22 operative survivors have died during follow-up. Death was due to myocardial infarction in 8 patients, cancer in 3, and other causes in 4; the cause was unknown in 4 patients. Actuarial 5-year and 10-year survival rates were 78% and 58%, respectively (Fig 5).

Comment

Extraanatomical extrathoracic bypass grafting is the procedure preferred by most surgeons to correct brachiocephalic arterial disease. The rationale for this attitude derives from the common belief that the transthoracic approach results in a prohibitive operative risk [8, 9].

The concept that thoracotomy represents an increased

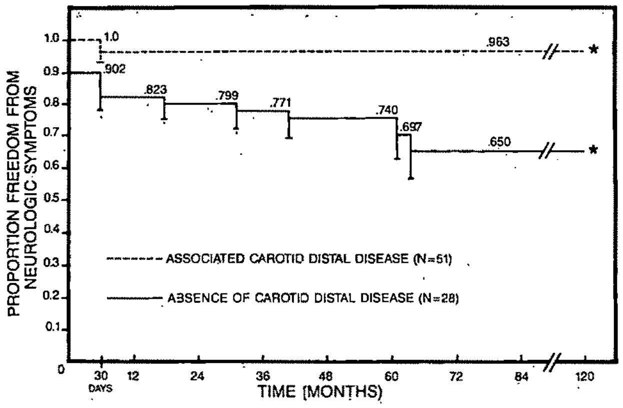

Fig 3. Actuarial freedom from neurological symptoms according to the presence or absence of associated distal carotid artery disease (Kaplan-Meier plot). Presence versus absence, p < 0.0001 (*) (log-rank test).

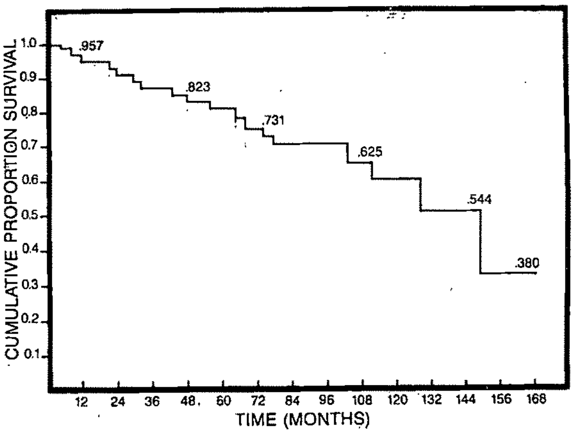

Fig 5. Actuarial survival (Kaplan-Meier plot).

surgical hazard may have been appropriate 31 years ago when DeBakey and associates [10] first inserted an aorta–subclavian–carotid artery bifurcation graft. At that time, operation on the chest was associated with a mortality rate of 20% and higher morbidity rates [11]. In 1967, Diethrich and colleagues [12] introduced carotid–subclavian artery bypass grafting as an alternative technique, which is easy to perform and has a low operative risk. This and many other extraanatomical interventions rapidly became very popular [8, 13–16], and the transthoracic bypass approach was almost completely abandoned by many centers. The hemodynamic and functional advantages of a transthoracic "anatomical" reconstruction were disregarded in view of the low risk of an extrathoracic "extraanatomical" procedure.

The recent developments in operative and anesthetic techniques, as well as in postoperative care, have markedly reduced the risk of thoracotomy. In our cardiovascular service, operations performed on brachiocephalic arteries through a transthoracic route were completely free from operative deaths, and even the morbidity was low. Furthermore, late functional results were excellent. Recently, Sandmann and co-workers [17] reported a series of 40 patients who underwent transthoracic revascularization with no operative deaths. Similar results have been reported by other experienced surgeons [1–4]. It appears that the risk/benefit ratio for the two approaches is now comparable.

On the basis of these considerations, the question can be raised as to why most surgeons continue to reject operation on the chest to treat proximal brachiocephalic arterial lesions. It seems that the choice of treatment is often based on the personal experience of the surgeon in performing a certain type of operation rather than the effective convenience of the technique. Patients with brachiocephalic arterial lesions are referred to different surgeons including general surgeons, cardiothoracic surgeons, vascular surgeons, and neurosurgeons. Each of them has enough experience to perform any vascular procedure in his or her surgical field, but not all of them are comfortable with a thoracotomy.

Thirty years ago, surgeons completing a general surgery residency also included in their training cardiac, thoracic, and vascular surgery. With the spreading of knowledge and techniques in each surgical area, separate specialties were created and broke away from each other. Each of these specialties now has its own separate training program and board certification. Cardiothoracic surgeons, very familiar with transthoracic interventions, are aware of the recent advances in thoracic surgery and do consider, when indicated, the possibility of a direct anatomical reconstruction. Conversely, other surgeons with limited experience in chest surgery do not.

We believe that, at present, the choice of operation between transthoracic or extrathoracic repair for proximal block of the branches of the aortic arch should not be influenced by any prejudice, but should be based on anatomical and clinical features of the individual patient. The two approaches should remain equal and viable alternatives. In the presence of multiple proximal arterial lesions and in patients with a good life expectancy, a transthoracic operation should be considered. In other instances, extrathoracic approaches are preferred depending on the location of the disease.

Rather than the type of surgical approach, two other variables were found to be strictly correlated to our results: the period in which the operation was performed and the presence of proximal and distal carotid disease. Operations performed after 1980 were associated with better functional results, a finding that perhaps demonstrates the importance of the experience of the surgeon in performing these interventions. Two perioperative deaths occurred after stroke, both in patients who underwent operation because of common carotid artery lesions and tandem distal lesions. Similarly, 2 of 100 patients in the series reported by Voght and associates [5] and 2 of 26 patients in the series of Moore and colleagues [6] died of stroke after treatment of common carotid artery lesions. It is noteworthy that in both reports, the deaths occurred in patients with associated bifurcation disease. Patients who are candidates for common carotid artery revascularization represent a high-risk population, and staged treatment should be planned in the presence of simultaneous lesions of the carotid bifurcation. Associated major stenosis of the carotid bifurcation was, in general, a significant risk factor. Surgeons should always consider the critical importance of a vascular evaluation of the whole cerebrovascular extracranial tree.

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REVIEW OF RECENT BOOKS

Gastroesophageal Reflux

Edited by Glyn G. Jamieson and André Duranceau
Philadelphia: W.B. Saunders, 1988
296 pp, illustrated, $49.00

Reviewed by Earle W. Wilkins, Jr, MD

This is the first major work on the entity of gastroesophageal reflux since that of Skinner, Belsey, Hendrix, and Zuidema in 1972, *Gastroesophageal Reflux and Hiatal Hernia*. Early in their book on gastroesophageal reflux, Jamieson and Duranceau comment: "'hiatus hernia' and 'gastroesophageal reflux' led more or less separate lives until 1951, when Allison coined the term 'reflux esophagitis' and associated the condition with 'sliding' hiatal hernia." The authors are to be commended on their preparation of the interchangeable usage of these two phenomena. The simple title of *Gastroesophageal Reflux* seems both appropriate and correct. Indeed, the words *hiatus hernia* do not appear in their table of contents.

This textbook is really a monograph consisting of 18 chapters (281 pages) on all aspects of gastroesophageal reflux from the theories of its pathogenesis, clinical features, and diagnosis to its complications and associated clinical conditions. Thirteen of the chapters are written by Jamieson or Duranceau themselves; nine other contributors have collaborated on five chapters. The geographical location of the authors, both surgeons, in Adelaide, Australia, and Montreal, Canada, certainly lends an interesting worldly flavor to the discussion of the problem, which has variously challenged and plagued physicians and surgeons for much of this century.

The strength of the book lies in its comprehensive presentation of each aspect of the subject, with careful mention of salient historical facts and voluminous references. There are 199, for instance, in the chapter on surgical treatment of gastroesophageal reflux disease. Literally no major contribution has been omitted. In many sections a brief summary is helpful. Exact definitions of terminology are stressed. Thus, reflux is considered *physiological gastroesophageal reflux* in the normal patient (one with neither symptoms nor histological esophageal changes) and *pathological gastroesophageal reflux* or *gastroesophageal reflux disease* in the symptomatic or complicated patient. The latter pair of interchangeable terms encompasses *reflux esophagitis* when histological abnormalities are proved in the esophagus and *reflux disorder* when symptomatic reflux only is encountered. This classification is very helpful in considerations involving choice of therapy.

A brief chapter on an attempt at staging of severity of gastroesophageal reflux is original and clinically impressive. Each of (1) the endoscopic findings, (2) histological evidence, (3) pH monitoring results, and (4) manometric studies is graded (E0–E3, H0–H3, R0–R2, and M0–M3) and then the ratings are combined to provide a classification of overall stages 0 through 4. As the authors state, "in an ideal world, each of these four areas would be studied in patients with severe reflux disease." I would add that they certainly should be considered if surgical intervention is contemplated.

The various options in surgical treatment are carefully described, although the illustrations are only sketches used to emphasize the differing technical concepts. The reader is advised to consult an original description before undertaking any given technique. A personal interappraisal by the authors of the three principal antireflux techniques in use today would have added substantial impact to this chapter. Their advice on less used procedures is sound: "it would seem best to avoid carrying out a fundoplication within the chest" and "at the present time [use of the Angelchik prosthesis] should still be considered experimental."

There are three particularly complete and helpful chapters: two on difficult entities presumably resulting from gastroesophageal reflux ("Columnar-Lined Esophagus" and "Management of Peptic Strictures") and the other on a phenomenon speculatively related thereto ("Lower Esophageal Ring").

In one sense, this book contains all that is known, certainly all one needs to know, about gastroesophageal reflux. In another, it only serves to illustrate both how slow has been progress in understanding the physiology of the lower esophageal sphincter (cf, Wilkins EW Jr. Current considerations of esophageal physiology, normal and abnormal. N Engl J Med 1957;257:24–31) and how illusive is a physiological breakthrough in the nonsurgical control and prevention of pathological reflux. Such a breakthrough would solve one of the admittedly more difficult aspects of this problem, reoperations for gastroesophageal reflux after a failed antireflux operation. The authors' advice regarding this particular problem is very sound.

Boston, Massachusetts

Anticipation of Bypass Surgery: Can It Induce Silent Myocardial Ischemia?

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Psychological stress has been demonstrated to induce myocardial ischemia. To determine whether stressful events before a coronary artery bypass grafting procedure precipitate myocardial ischemia, silent or symptomatic, and whether this can have an effect on the prognosis, 26 patients were evaluated before a bypass operation with continuous Holter monitor recording. Specific events monitored were signing surgical consent, receiving preoperative medications, shaving and preparing, and transfer to the operating room. A positive Holter result was defined as an ST segment depression of 1 mm or more lasting one minute or longer. Six patients (23%) were found to have one or more episodes of substantial ST segment depression, with a total of ten episodes lasting 208 minutes recorded. All episodes were silent and not associated with an increase in mean heart rate. The majority of episodes occurred randomly, although three episodes did occur between 5 and 6 AM at the time of transport to the operating room. This appeared to be related more to the circadian rhythm than to the stress of transport. No perioperative or postoperative myocardial infarctions occurred, and all patients were alive at 30 days. In conclusion, silent myocardial ischemia present in the immediate preoperative period does not appear to be related to specific preoperative events. Frequency of early morning ischemia may warrant changes in the medication schedule to provide additional protection during these hours.

(Ann Thorac Surg 1989;47:586–8)

Specific events such as signing surgical consent, receiving preoperative medications, shaving and preparing, and transfer to the operating room can cause increased stress in patients who are to undergo coronary artery bypass grafting. Such psychological stress has been demonstrated to induce active myocardial ischemia, particularly asymptomatic [1–3], and potentially can increase the risk of perioperative and postoperative cardiac events. Using continuous ambulatory monitoring, we evaluated the incidence and importance of preoperative myocardial ischemia in patients undergoing coronary artery bypass grafting. We specifically evaluated whether particular stressful preoperative events are associated with increased myocardial ischemia.

Material and Methods

Twenty-six patients (20 men and 6 women with a mean age of 62.9 ± 9.4 years) were randomly chosen from a daily list of coronary artery bypass patients. Nineteen patients had unstable angina, and 7 had chronic stable angina. Patients had a Holter monitor placed on the day before operation. They were provided a diary to record any symptoms and were instructed to press the Holter trigger if any occurred. The monitor was removed on arrival in the operating room holding area. For each patient, the time of four preoperative events was noted: signing surgical consent, receiving preoperative medications, shaving and preparing, and transfer to the operating room.

The anesthesia preoperative orders were morphine sulfate, 7.0 mg intramuscularly, and scopolamine hydrobromide, 5.0 mg intramuscularly, both given on call. The surgical orders were dipyridamole, 100 mg orally at 6 PM and 12 AM, cefazolin sodium, 1 g intramuscularly on call, and nitroglycerin ointment 2%, 3.75 cm (1.5 inches) to the left arm on call.

Patients were followed for the development of recurrent perioperative and postoperative symptomatic myocardial ischemia, major ventricular arrhythmias, myocardial infarction, or death. Myocardial infarction was diagnosed when an elevated creatine kinase level with a positive MB fraction was associated with new major Q waves in two contiguous leads. Patients were followed for 30 days.

Ambulatory ST segment recordings were obtained using Spacelabs model 90201 (Spacelabs, Redmond, WA). Leads II and CM5 were monitored in each patient. Data retrieval programs allowed 24-hour ST segment and heart rate trend plots to be generated. All changes observed in the trend plots were verified by examining electrocardiograms at 25 mm/s obtained by direct writing from the tape recordings. The electrocardiographic strips were then analyzed to find the time of onset and the duration of substantial ST segment depression and mean heart rate for each episode. An episode of ischemia was defined as 1 mm or more of horizontal or downsloping ST segment

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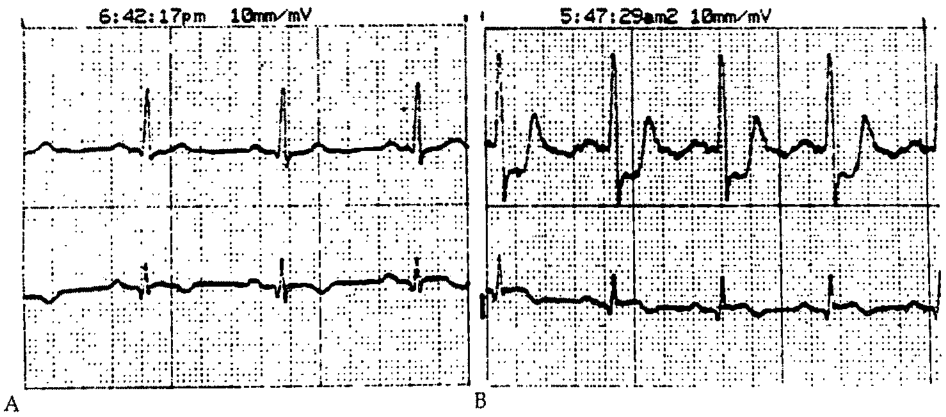

Fig 1. (Patient 23.) Reproduction of two-channel Holter recording, baseline (left) and asymptomatic episode of 4-mm ST segment depression (right).

depression at 80 ms from the J point lasting one minute or more. Data were analyzed using Student's *t* test.

Results

All tapes were suitable for analysis. Mean recording time was 16.5 ± 3.8 hours. No patient had ST segment elevations recorded. Six patients (23%) had one or more episodes of ST segment depression (Fig 1); a total of ten episodes lasting 208 minutes were recorded. All the episodes were silent and were not associated with major changes in heart rate. Three patients had ischemic episodes between 5 AM and 6 AM at the time of transfer to the operating room. All the other episodes occurred randomly during the day and were not associated with any specific event.

There were no differences in the groups with and without silent ischemia in regard to the presence of

Table 1. Patient Profiles

Patient No.	Sex	Angina Status	Nitrate	β-Blocker	Calcium Blocker	Anatomy	Silent Ischemic Episodes
1	Female	Unstable	Yes	No	Yes	Two-vessel disease	0
2	Male	Unstable	Yes	No	Yes	Three-vessel disease	0
3	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	0
4	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	0
5	Male	Unstable	Yes	No	Yes	Three-vessel disease	1 (8 min)
6	Male	Unstable	Yes	No	Yes	Two-vessel disease	0
7	Male	Stable	Yes	Yes	No	Three-vessel disease	0
8	Male	Stable	Yes	No	Yes	Three-vessel disease	0
9	Male	Unstable	Yes	No	Yes	Two-vessel disease	0
10	Female	Unstable	Yes	No	Yes	Three-vessel disease	1 (3 min)
11	Male	Unstable	Yes	Yes	Yes	Two-vessel disease	2 (14, 25 min)
12	Male	Stable	Yes	Yes	Yes	Two-vessel disease	0
13	Male	Stable	Yes	Yes	No	Three-vessel disease	0
14	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	0
15	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	0
16	Female	Unstable	Yes	No	Yes	Three-vessel disease	0
17	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	0
18	Male	Unstable	Yes	No	Yes	Three-vessel disease	0
19	Female	Stable	Yes	No	Yes	Three-vessel disease	0
20	Male	Stable	Yes	Yes	Yes	Three-vessel disease	1 (15 min)
21	Female	Stable	Yes	No	Yes	One-vessel disease	4 (31, 27, 20, 36 min)
22	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	0
23[a]	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	1 (29 min)
24	Male	Unstable	Yes	Yes	Yes	Three-vessel disease	0
25	Female	Unstable	Yes	No	Yes	Three-vessel disease	0
26	Male	Unstable	Yes	No	Yes	Two-vessel disease	0

[a] This is the patient whose Holter monitor recording is shown in Figure 1.

unstable angina, use of antianginal medications, or severity of coronary artery disease (Table 1). No patient had critical postoperative ventricular arrhythmias or myocardial ischemia. No new myocardial infarctions were recorded. All patients were alive 30 days postoperatively.

Comment

Ambulatory monitoring studies have demonstrated that silent myocardial ischemia can occur during relatively nonexertional activities such as office work, telephone conversations, and other predominantly mental activities [1]. A recent study by Freeman and co-workers [2] demonstrated that the psychological and emotional stress of discussing the results of coronary angiography and the need for operation can induce silent ischemia. Specific routine events—signing surgical consent, receiving preoperative medications, shaving and preparing, and transfer to the operating room—are also highly stressful and could potentially induce myocardial ischemia in patients being prepared for coronary artery bypass grafting.

Our study found a 23% incidence of silent ischemia in the preoperative period, but most of the episodes recorded occurred randomly throughout the day and were not associated with any specific event. Three patients manifested silent ischemia on transfer to the operating room, but these episodes all occurred during the one-hour period 5 to 6 AM. Although it is not certain that these episodes were not induced by the stress of transportation, they could more easily be explained by the reported increase in myocardial ischemia in the early morning hours [4]. Early morning increases in plasma catecholamine values can cause increased blood pressure, heart rate, and ventricular contractility, all of which can increase myocardial oxygen needs [5]. The increase in catecholamines can also lead to increased coronary tone and altered coronary blood flow. Changes in platelet function with increased platelet aggregability [6] and decreases in function of the fibrinolytic system [7] can result in a hypercoagulable state and further contribute to diminished coronary blood flow. Of note, none of the 10 patients in the study who were transported to the operating room after 9 AM exhibited ST depressions with transportation.

Yousif and associates [8] also evaluated preoperative ambulatory recordings in patients undergoing a bypass procedure. These investigators found an 18% incidence of ischemia in patients receiving routine preoperative care, which is similar to our findings. As in our study, the presence of silent ischemia was not associated with a higher frequency of perioperative infarctions. Their study did not evaluate specific preoperative events for their role in inducing silent myocardial ischemia.

In conclusion, silent myocardial ischemia present in the preoperative period does not appear to be related to specific routine preoperative events. However, its increased incidence between 5 and 6 AM, an apparent manifestation of the circadian rhythm, suggests a possible increased risk of coronary artery bypass grafting in the early morning hours. Changes in the medication schedule to provide additional protection during these hours should be considered.

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Anticoagulant Therapy in Children With Prosthetic Valves

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The purpose of this study was to evaluate the effectiveness and complications of several types of anticoagulant therapy in children with prosthetic valves. During a 7-year period ending April 1985, 130 children aged 1 to 19 years underwent left-sided valve replacement. Operative mortality was 3%, 5%, and 9%, respectively, for aortic, mitral, and aortic and mitral valve replacement. Among the 123 survivors, 32 (26%) had had aortic, 71 (58%) had had mitral, and 20 (16%) had had aortic and mitral valve replacement. Follow-up ranged from 2 months to 8.2 years, a total of 544 patient-years. The survivors were divided into three groups based on anticoagulant treatment: warfarin sodium, aspirin plus dipyridamole, and no anticoagulants. Among the patients who had aortic valve replacement, thromboembolic complications developed in 2.5% (2.5/100 patient-years) of the aspirin plus dipyridamole group and 5% of the group given no anticoagulants. Only the warfarin group (4%) experienced bleeding complications. Among the patients having mitral valve replacement, thromboembolic complications developed in 4% of the warfarin group, 3% of the aspirin plus dipyridamole group, and 11% of the no anticoagulant group. In addition, 2% of patients in the warfarin group experienced severe bleeding. Two fatal cerebrovascular accidents occurred, both in the aspirin plus dipyridamole group. Patients who received a mitral heterograft were not prescribed any anticoagulant medications, and no thromboembolic complications developed. Among patients having double-valve replacement, complications developed in 5% of the warfarin group and 27% of the group given no anticoagulants. Based on these data, aspirin plus dipyridamole appears adequate for patients having aortic valve replacement, whereas warfarin is required in patients having double-valve replacement. Patients having mitral valve replacement with heterografts require no anticoagulation, but those with mechanical valves may need warfarin anticoagulation. There are not adequate data to evaluate the safety and efficacy of the combined use of warfarin and a platelet-inhibiting drug in children.

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Although it occurs less frequently in children than in adults, thromboembolism continues to be a major problem after insertion of prosthetic valves in children. Consequently, anticoagulation with warfarin sodium is generally recommended [1–5]. However, increased susceptibility to trauma, poor compliance, and difficulties in maintaining long-term anticoagulation complicate the prolonged use of oral anticoagulants in children. The purpose of this study was to evaluate the efficacy and complications of various forms of anticoagulant therapy in children with prosthetic valves to formulate recommendations for the most useful anticoagulant regimen.

Material and Methods

During a 7-year period ending April 1985, 130 children underwent left-sided valve replacement at the King Faisal Specialist Hospital and Research Center. The operative mortality was 3%, 5%, and 9%, respectively, for aortic, mitral, and combined aortic and mitral valve replacement. Of the 123 surviving children aged 1 to 19 years, 32 (26%) had had the aortic valve replaced, 71 (58%) had had the mitral valve replaced, and 20 (16%) had had both valves replaced. The age and sex distribution is listed in Table 1.

Ninety-three percent of the lesions were rheumatic in origin, 6% were congenital, and 1% were infectious. A total of 143 valves were replaced. Thirty-three (23%) of the replacement valves were heterografts, and all but 1 were in the mitral position. Of the 110 mechanical valves, 16 (15%) were Björk-Shiley valves, 34 (31%) were Smeloff-Cutter valves, 30 (27%) were Beall valves, and 30 (27%) were St. Jude Medical valves. Follow-up ranged from 2 months to 8.2 years (mean follow-up, 4.5 years) and totaled 544 patient-years.

The 123 survivors were divided into three groups based on anticoagulant therapy: warfarin, aspirin plus dipyridamole, and no anticoagulants. No anticoagulant medications were prescribed for patients with porcine heterografts. Some form of anticoagulant therapy was prescribed for all patients with mechanical prosthetic valves. Some patients did not follow the prescribed treatment and discontinued the medications on their own; they were included in the no anticoagulant group. Warfarin dosage was adjusted to achieve a prothrombin time of 180% to 200% of control when human brain thrombo-

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Table 1. Age and Sex Distribution of Surviving Patients

Age (yr)	Male	Female	Total
1–5	1	2	3
6–10	6	10	16
11–15	24	24	48
16–19	28	28	56
Total	59	64	123

plastin was used in the assay. More recently, when reptile thromboplastin was used for the prothrombin time assay, 150% of control prothrombin time was sought. The patients receiving warfarin were followed in our special anticoagulant clinic at 2-week intervals initially and at 4-week intervals subsequently to adjust the warfarin dose. Aspirin was prescribed at a dosage of 10 mg/kg/day, but on final analysis, the dosage was 12.0 ± 4.5 mg/kg/day. Two to 5 mg/kg/day of dipyridamole was prescribed, and the children received 3.0 ± 1.1 mg/kg/day.

Patients were followed in the pediatric cardiology clinic at 6- to 12-week intervals initially and at 6- to 12-month intervals subsequently, and were monitored for thromboembolic and bleeding complications. A thromboembolic event was presumed to be present if there was evidence of valve obstruction from clot formation, stroke, or peripheral pulse loss. Clinically significant bleeding was considered to be present if the bleeding required hospitalization or blood transfusion, or resulted in death. Mild bleeding episodes not requiring hospitalization or change of therapy were not used for calculating bleeding incidence.

The actuarial method of Grunkemeier and Starr [6] was used for expressing survival and complication-free survival rates. Thromboembolic and bleeding complications were expressed as linearized rates, that is, the number of events per 100 patient-years, expressed as a percentage [7]. Group comparisons of thromboembolic rates were made by means of the χ^2 test. Statistical significance was set at a p value of less than 0.05.

Results

The 123 children surviving valve replacement were followed for 2 months to 8.2 years. Five-year actuarial survival was 94% for aortic, 88% for mitral, and 75% for double-valve replacement. Major events included reoperation in 18 patients (with 3 deaths), progressive myocardial failure in 4, and sudden unexpected death in 2. Thromboembolic and bleeding complications will be discussed later. The 5-year actuarial complication-free (major event-free) survival was 93% for aortic, 80% for mitral, and 52% for double-valve replacement.

Of the 544 patient-years of follow-up, 175 patient-years represented porcine heterograft valve follow-up. None of the patients with heterograft valves received anticoagulant therapy. There were no thromboembolic or bleeding complications in this group of patients during follow-up. The remaining 369 patient-years of follow-up represented mechanical prosthetic valves. The warfarin group had 111 patient-years, the aspirin plus dipyridamole group had 175 patient-years, and the no anticoagulant group had 83 patient-years.

Among patients with an aortic valve prosthesis, thromboembolic complications developed in 2.5% of the aspirin plus dipyridamole group and 5.1% of the no anticoagulant group. Four percent of the warfarin group had bleeding complications (Fig 1). There was no significant difference ($p > 0.1$) in the linearized rates of thromboembolic and bleeding complications between the groups. Seventy percent of the replaced aortic valves were Smeloff-Cutter valves, and 25% were St. Jude Medical valves. All the thromboembolic complications occurred in patients with the Smeloff-Cutter valve. Neither the bleeding nor the thromboembolic episodes resulted in death or permanent sequelae.

Among patients with a mechanical prosthetic mitral valve, 4.2% of the warfarin group ($p > 0.1$), 3.4% of the aspirin plus dipyridamole group ($p > 0.1$), and 10.8% of the no anticoagulant group ($p < 0.01$) had thromboembolic complications. In addition, 2.1% of the warfarin group sustained severe bleeding complications (see Fig 1). The types of valve used were Beall (40%), St. Jude Medical (40%), and Björk-Shiley (15%). Seventy-five percent of all thromboembolic complications related to mitral valve replacement occurred with Beall prostheses, and 12.5% each, with St. Jude Medical and Björk-Shiley prostheses. Although there was a higher rate of total complications in the warfarin group, both deaths related to thromboembolic complications occurred in the aspirin plus dipyridamole group.

Among patients having double-valve replacement, 5.1% of the warfarin group and 27.3% of the no anticoagulant group ($p < 0.01$) sustained thromboembolic complications. In addition, bleeding complications developed in 2.6% of the warfarin group (see Fig 1).

Comment

To date, there is no consensus in regard to the type of anticoagulant regimen for prevention of thromboembolic

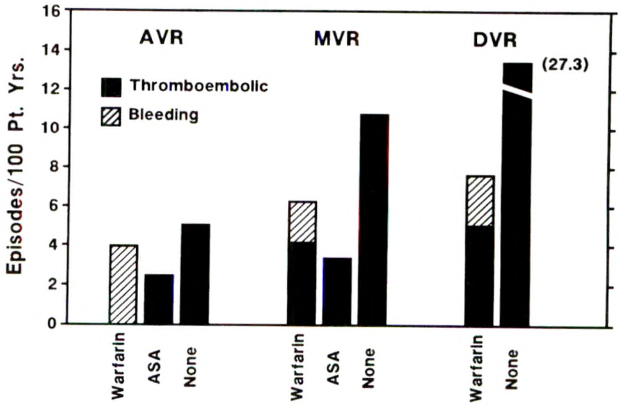

Fig 1. Thromboembolic and bleeding complications, expressed as episodes per 100 patient-years (Pt. Yrs.), based on anticoagulant treatment (warfarin sodium, aspirin plus dipyridamole [ASA], and no anticoagulants) and type of valve replacement (aortic valve [AVR], mitral valve [MVR], and double-valve replacement [DVR]).

complications after prosthetic valve replacement in children. The recommendations range from no anticoagulant therapy [8–10], platelet-inhibiting drugs [11–14], and warfarin alone [1–5, 15, 16] to a combination of warfarin and an antiplatelet agent [17]. We will attempt to formulate recommendations for anticoagulant therapy based on our data and the data reported in the literature. Our comments will be confined to left-sided prosthetic valve replacement because we did not include patients having right-sided prosthetic valve replacement in the study population.

Heterografts

Although there is no consensus, it is generally recommended that warfarin be given to adult patients for the first 3 months after insertion of a bioprosthesis [1, 18]. If risk factors for the development of thromboembolism such as a mitral bioprosthesis, atrial fibrillation, left atrial thrombus, previous emboli, and a large left atrium are present [1, 18], warfarin is continued beyond the 3-month period. During one 175 patient-years of follow-up of children with left-sided porcine heterografts, no thromboembolic event occurred, and these patients were prescribed no anticoagulant therapy. This finding and the low rate of thromboembolic complications in children [5, 8, 19–23] lead us to recommend that no anticoagulants be given to infants, children, and adolescents with bioprosthetic valves. However, it would seem reasonable to suggest anticoagulation with warfarin if risk factors such as atrial fibrillation, left atrial thrombus, previous emboli, and a markedly enlarged left atrium are present.

Mechanical Valves

AORTIC VALVE REPLACEMENT. In this study, there was a lower incidence of complications in the aspirin plus dipyridamole group compared with the warfarin and the no anticoagulant groups, although the linearized rates are not significantly different. The minor thromboembolic events did not result in death or permanent sequelae. Based on these data and those in the literature [11–14], we recommend only antiplatelet drugs (aspirin plus dipyridamole) as the therapy of choice after aortic valve replacement with mechanical valves in children. Such a recommendation is supported by the theoretical basis of the mechanism of formation of arterial thrombi in the aortic valve area with high-velocity blood flow; the interaction of platelets with the prosthetic valve surface causes adhesion and aggregation of platelets onto the prosthetic valve with subsequent fibrin deposition [24, 25]. The platelet aggregates can become detached and embolize [24, 25]. By inhibiting platelet adhesion, platelet-inhibiting drugs may prevent thromboembolic complications of aortic valve prostheses.

MITRAL VALVE REPLACEMENT. In this study, the linearized rates of thromboembolism or bleeding in the warfarin and the aspirin plus dipyridamole groups are lower than those in the no anticoagulant group. The logical conclusion is that the patients undergoing mitral valve replacement need some form of anticoagulation. The slightly lower rates in the aspirin plus dipyridamole group than in the warfarin group could tempt one to recommend aspirin plus dipyridamole as the preferred anticoagulant regimen. However, that recommendation is clouded by the fact that both deaths related to an embolic event occurred in the aspirin plus dipyridamole group. Therefore, we hesitate to recommend only platelet-inhibiting drugs for patients with a mitral prosthesis. Patients with a mechanical mitral valve probably should receive warfarin anticoagulation. The theoretical basis of formation of thrombus [24] in the low-flow mitral area (red thrombus in contrast to white thrombus in the aortic valve area) would also support the use of warfarin in these patients.

Because warfarin does not abolish thromboembolic complications, the adding of a platelet-inhibiting drug to a warfarin regimen has been tried in adult patients and the results have been favorable [18, 25–27]. Limited studies in children [17] also suggest favorable results. However, the incidence of bleeding is prohibitively high when a combination of warfarin and an antiplatelet agent is used [12]. Additional studies to confirm the efficacy and safety of this combined drug approach in children are needed before it can be recommended for routine use.

DOUBLE-VALVE REPLACEMENT. Our results suggest that warfarin is far superior to no anticoagulant treatment in preventing thromboembolic complications in children undergoing both mitral and aortic valve replacement. The high incidence of thromboembolism in the no anticoagulant group cannot be explained solely by the additive risk of another mechanical valve. More important is the persistently reduced cardiac function, even after surgical repair, which was encountered more frequently in the double-valve replacement group compared with the single-valve replacement groups. The importance of warfarin treatment, especially in hemodynamically compromised patients, in reducing the risk of embolic complications is clearly reflected in our results. The considerations as to whether an antiplatelet agent should be added to warfarin or not are similar to those for isolated mitral valve replacement. Until more data on use of this combination of drugs are available, warfarin should be used in patients having double-valve replacement.

Summary

In summary, (1) bioprostheses in children do not necessitate anticoagulation unless a risk factor for a thromboembolic event is present; (2) aspirin plus dipyridamole is adequate for mechanical aortic valves; (3) warfarin may be needed in patients with a mitral valve prosthesis; (4) warfarin anticoagulation should be prescribed for patients having double-valve replacement; and (5) there are not adequate data to evaluate the effectiveness and safety of the use of an antiplatelet drug with warfarin in children with a mitral valve prosthesis or mitral and aortic valve prostheses.

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Repair of Large Muscular Ventricular Septal Defects in Infants Employing Left Ventriculotomy

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The approach to muscular ventricular septal defect has been controversial. Traditional approaches have included pulmonary artery banding or right ventriculotomy. Left ventriculotomy has been employed in older children because of the ease of exposure in the absence of trabeculations, but concern has been raised regarding potential loss of left ventricular function. Four infants less than 4 months of age underwent repair of a large muscular ventricular septal defect by left ventriculotomy. One infant had no associated defects; 2 had undergone previous coarctation repair (1 with pulmonary artery banding); and 1 had a large secundum atrial septal defect. All had congestive heart failure refractory to maximal medical management. All patients survived, and there was no myocardial dysfunction. Echocardiographic indices of ventricular function 3 to 24 months postoperatively were normal (mean shortening fraction, 32.5%). Left ventriculotomy with patch closure of the ventricular septal defect provides a simple approach to a large muscular ventricular septal defect in infants with heart failure.

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Large muscular ventricular septal defects (VSDs) alone or in combination with other cardiac defects are difficult to close from a right atrial or right ventricular approach. If medical therapy is unsuccessful, pulmonary artery banding has frequently been used rather than primary closure of the defect itself. Left ventriculotomy has been used to close a VSD in older children and adults with postinfarction or posttraumatic VSD [1–3]. We present data on 4 consecutive infants with a large muscular VSD in whom the left ventricular approach for closure was employed.

Material and Methods

The 4 patients were infants less than 4 months of age, each with congestive heart failure refractory to medical management (Table 1). All were term infants who were seen with marked congestive heart failure by the time they were 2 weeks of age. Cardiac catheterization demonstrated large left-to-right shunts and elevated pulmonary artery pressures (Table 2). Failure to grow and respiratory insufficiency unresponsive to medical therapy were the indications for surgical closure of the VSD. In 1 patient, a pulmonary artery band was placed at the time of coarctation repair, but heart failure persisted.

All operations were performed through a median sternotomy. Cardiopulmonary bypass was accomplished with a single venous cannula through the right atrial appendage and an arterial cannula in the ascending aorta. Systemic hypothermia to 22°C was induced, and the aorta was cross-clamped. A single dose of crystalloid cardioplegic solution was administered in the ascending aorta. Circulatory arrest was not required. A short apical left ventriculotomy was performed, with care taken to avoid the left anterior descending coronary artery and the last large diagonal branch. The VSD was noted to be a single large muscular defect located in the midseptum in each patient. Repair was accomplished with a bovine pericardial patch (because of its ease of handling) and 5-0 polypropylene running sutures. The ventriculotomy was closed with a running two-layer suture line of 5-0 Prolene (Ethicon, Inc, Somerville, NJ) without buttress material. The pulmonary artery band was removed in the 1 patient, but the pulmonary artery did not require a patch.

Results

The postoperative course in all patients was uncomplicated. All were weaned from cardiopulmonary bypass without difficulty. One infant (patient 4) required no inotropic support, and the others received intravenous inotropic support (dobutamine hydrochloride or dopamine hydrochloride; dosage range, 3 to 10 μg/kg/min) for an average of 2.2 days (range, 1.9 to 2.4 days). The respiratory status of all patients improved dramatically. By the fourth postoperative day, all tubes were removed (average length of intubation, 2.3 days). None of the patients exhibited ventricular arrhythmias or ventricular dysfunction by echocardiographic evaluation during the postoperative period. The average postoperative stay was 12 days.

All patients have done well during follow-up, which ranges from 1 month to 2 years. The infants have exhibited improved growth with resolution of the respiratory problems except for patient 1, who has chronic reactive airway disease. Left ventricular function is normal by echocardiographic estimation of shortening fraction.

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Table 1. Clinical Features of Infants With Muscular Ventricular Septal Defect Repaired via Left Ventriculotomy

Patient No.	Age (wk)	Weight (kg)	Preoperative Condition	Associated Lesions	Postoperative Stay (days)
1	7	3.1	Assisted ventilation	Aortic coarctation	15
2	8	3.9	Assisted ventilation	Aortic coarctation	11
3	11	4.3	CHF, failure to thrive	None	9
4	15	4.3	CHF, failure to thrive	Atrial septal defect	13

CHF = congestive heart failure.

Table 2. Hemodynamic Data From Infants With Muscular Ventricular Septal Defect Repaired via Left Ventriculotomy

Patient No.	Pulmonary/ Systemic Flow Ratio	Mean Pulmonary Artery Pressure (mm Hg)	Mean Systemic Artery Pressure (mm Hg)	Preoperative Shortening Fraction[a] (%)	Postoperative Shortening Fraction (%)
1	6.5:1	32[b]	63	33	35
2	. . .[c]	. . .[c]	. . .[c]	19	33
3	9.1:1	45	62	33	32
4	4.1:1	40	55	35	30

[a] The normal values range from 28% to 42%. [b] This was distal to the pulmonary artery band. [c] Catheterization was unsuccessful. Pulmonary hypertension was present by echocardiographic evaluation. There was abnormal pulmonary valve motion with decreased A dip and increased pulmonary systolic time interval of 0.4 (normal, <0.3).

None have clinical evidence of residual left-to-right shunts or congestive heart failure.

Comment

Muscular VSDs account for only a small portion of the total number of VSDs requiring surgical intervention [4]. Small muscular defects without hemodynamic significance often close spontaneously [5]. Large muscular defects can produce pulmonary hypertension, pulmonary edema, respiratory insufficiency, and failure to grow. Pulmonary artery banding and closure from the right-sided approach have been only moderately successful. The coarse trabeculations in the right ventricle can preclude complete visualization of the defect [6]. Closure of a muscular defect through the left ventricle was reported by Aaron and Lower [7] in 1975. Subsequently there have been reports [8–10] concerning use of this approach in older infants and children with low morbidity and mortality. We believed that this surgical approach could be adapted to infants.

Four infants with muscular defects of the ventricular septum underwent closure of the defect at less than 4 months of age using the left ventriculotomy approach. There were no operative deaths, and the clinical condition of each infant markedly improved. No major left ventricular dysfunction was identified by echocardiography. The subsequent clinical course has been unremarkable. The postoperative course was not different from that in our experience with infants in whom the VSD (perimembranous or inlet) was closed through a right atriotomy. Use of the left ventricular approach for closure of a muscular VSD allows complete visualization of the defect and enhances the chance of a complete closure. The technique is simple and well tolerated in infants. This approach is now our method of choice for care of the infant with a large muscular VSD refractory to medical management.

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Fifteen-Year Results of Coronary Artery Bypass for Isolated Left Anterior Descending Coronary Artery Disease

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During 1971 through 1975, 266 patients underwent primary coronary artery bypass grafting for occlusive disease confined to the left anterior descending coronary artery. Actuarial survival at 15 years was 72.7% with 60% of survivors being free from angina. Although the cause of death was cardiac related in 50% of the patients who died, survival was comparable with that of an age-matched and sex-matched general population. During follow-up, 48 secondary or tertiary repeat coronary artery bypass as well as 44 percutaneous transluminal coronary angioplasty procedures were performed. Acute event–free status (freedom from acute myocardial infarction, repeat coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or death) persisted at 15 years in 43.2% of patients. The differences in survival when patients were segregated according to age, sex, number of grafts performed, or graft conduit (internal mammary artery versus vein) were not significant. However, comparison of graft conduits revealed a significantly better ($p = 0.02$) overall acute event–free survival when the internal mammary artery was used.

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There has been continuing reevaluation of the effectiveness of coronary artery bypass grafting (CABG) for various presentations of coronary artery occlusive disease since the initial application of this surgical technique approximately two decades ago. One category of patients for whom the relative merits of CABG versus those of nonoperative treatment are not clearly defined is the patient with isolated left anterior descending coronary artery (LAD) obstruction. The present report is based on the late follow-up of a consecutive series of patients who underwent CABG for isolated LAD disease.

Material and Methods

During the 5-year period ending December 31, 1975, 266 patients underwent a primary coronary artery bypass procedure for isolated obstructive disease of the LAD at Saint Luke's Hospital. No patient had severe (≥50% stenosis of luminal diameter) obstructive lesions of the main left, circumflex, or right coronary artery or their major branches. In many patients, however, certain of these other coronary arteries were involved to a lesser degree by coronary artery occlusive disease.

In 260 patients (97.7%), the immediate indication for operation was angina or a recent ischemic event. The angina was class III or IV (New York Heart Association) in 214 patients. In 194 patients, the angina was characterized as unstable, indicating substantial increase in severity or frequency, or both, during the 6 weeks immediately before operation; in 69 of the 194 patients, angina was designated as severely unstable because of the prolonged and severe nature of spontaneously occurring episodes. Operation was performed early (14 to 30 days) after a recent myocardial infarction (MI) in 6 patients and as an emergency during early evolution (< six hours) of an acute MI in 3 others. Six patients were asymptomatic during the 6-week period before operation.

The age of the patients at the time of operation ranged from 32 to 76 years with a mean of 54.5 years. Sixty-eight (25.6%) were women. Left ventricular end-diastolic pressure measured at preoperative catheterization (before left ventriculography) was less than 10 mm Hg in 31% of the patients, 10 to 19 mm Hg in 58%, 20 to 29 mm Hg in 9%, and greater than 30 mm Hg in 2%.

Cardiopulmonary bypass (disc or bubble oxygenator), mild systemic hypothermia (30°C), and ischemic cardiac arrest (single or intermittent) were the operative techniques used in each patient. No patient with isolated LAD disease, other than those in whom a major cardiac procedure was performed concomitantly, was excluded from the study. A total of 295 distal anastomoses (1.1 per operation) to the LAD proper, its branches, or both, were performed. Single CABG was performed in 238 patients, double CABG in 27, and triple CABG in 1 patient. The internal mammary artery (IMA) was the bypass conduit in 39 patients, the cephalic vein in 1 patient, and the saphenous vein in all other patients. An endarterectomy of the LAD was performed in conjunction with saphenous vein bypass grafting in 3 patients. Mean graft flow (measured in the operating room) was 95 mL/min in the vein grafts and 55 mL/min in the IMA grafts.

There was postoperative evolution of a new transmural MI in 12 patients (4.5%). By electrocardiographic localiza-

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Table 1. Relationship of Postoperative Peak Serum Glutamic-Oxaloacetic Transaminase Levels to Occurrence of Acute Myocardial Infarction[a,b]

Serum Glutamic-Oxaloacetic Transaminase (IU/mL)	No. of Patients	Incidence of Acute Myocardial Infarction[c]
<50	46	0
50–99	169	3 (1.8)
100–199	35	2 (5.7)
200–299	8	3 (37.5)
>300	7	4 (57.1)

[a] Numbers in parentheses are percentages. [b] The peak level was measured on the first and third postoperative days in 265 patients. [c] These are transmural infarctions by electrocardiographic criteria.

tion, the infarct was anterior in 9 patients, inferior in 2, and lateral in 1 patient. The postoperative level of serum glutamic-oxaloacetic transaminase was measured routinely on the first and third postoperative days. The relationship of the peak elevations of this enzyme to the incidence of transmural MI is shown in Table 1. Two patients who did not demonstrate electrocardiographic evidence of a transmural MI exhibited low cardiac output syndrome during the early postoperative period. Venous thromboembolic episodes occurred in 12 patients, sepsis (wound, pulmonary, systemic, or a combination of these) in 6 patients, central nervous system injury in 2 patients, and other miscellaneous complications, none of which caused permanent damage, in 7 additional patients. There were no operative (≤30 days) deaths.

Late periodic follow-up was obtained by office visits, evaluation by the patient's cardiologist or physician, telephone interviews with the patient or family, or a combination of these. Anginal status was determined and classified annually when possible, according to the New York Heart Association classification. Tabulations were made of the linearized annual incidence (occurrences/100 patient-years, expressed as a percentage) of late (>30 days) acute MI, repeat CABG, percutaneous transluminal coronary angioplasty (PTCA), and death (from any cause). Special effort was made to establish the cause of death in each instance. Deaths within 30 days of an acute MI, repeat CABG, or PTCA were tabulated as event-related deaths.

Survival curves and event-free curves (freedom from acute MI, repeat CABG, PTCA, and death) were derived by the life-table method for the entire group as well as for subsets segregated by age, sex, number of coronary artery bypass grafts constructed, and the conduit (IMA versus vein) used for CABG [1]. The significance of differences observed in survival curves obtained from these patient subsets was calculated using a modified Wilcoxon signed rank test [2]. Overall survival was compared with that expected in an age-matched and sex-matched general population based on United States decennial life tables for 1979 to 1981 [3]. The significance of differences observed at 15 years postoperatively in the event-free status of the subsets was determined by calculating the p value using the two-tailed Z statistic [1].

Table 2. Anginal Status of Late Survivors

Anginal Class[a]	Postoperative Follow-up (yr)		
	5 (%)	10 (%)	15 (%)
I	68.6	64.1	60
II	19.2	18.6	4
III, IV	12.2	17.3	36

[a] This is according to the New York Heart Association classification.

Results

No patient was lost to follow-up. Each patient was followed to the time of death, or for at least 12 years for current survivors. The longest follow-up was 16.5 years. A total follow-up of 3,164 patient-years (mean follow-up, 11.9 years) was obtained.

The percentage of surviving patients who were free from angina at 5, 10, and 15 years postoperatively was 68.6%, 64.1%, and 60%, respectively (Table 2). There was a progressive increase in the proportion of survivors who manifested class III or IV angina to 36% at 15 years postoperatively.

The linearized annual incidence of acute MI (fatal or nonfatal) was 2.4%; repeat CABG, 1.5%; PTCA, 1.4%; and death (from any cause), 2.0%. It should be noted that PTCA was first used for myocardial revascularization at our institution in 1980.

Overall patient survival up to 15 years is shown in Figure 1. Survival was 95.5% at 5 years, 86.1% at 10 years, and 72.7% at 15 years. It is interesting that these individuals have survived as well as those in an age- and sex-matched general population.

The causes of death are tabulated in Table 3. Where determinate, 50% of the deaths were due to cardiac-related causes. Seven of these deaths occurred 5.8 to 11.5 years postoperatively (mean time, 8.2 years) as complications of attempts at myocardial revascularization (repeat

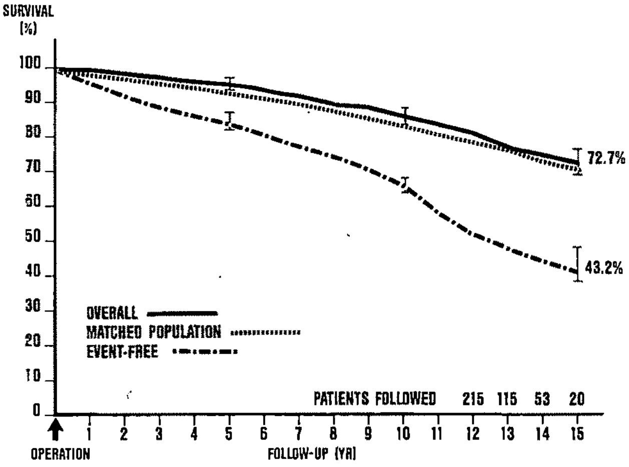

Fig 1. Overall survival (± standard error) at 15 years was 72.7%. Projected 15-year survival of age-matched and sex-matched general (white) population in the United States is 71.2%. Overall event-free survival (± standard error) at 15 years was 43.2%. Number of patients followed for 12 years or more is shown.

Table 3. Causes of Death[a]

Cause	No. of Patients
Cardiac	31 (49.2)
Acute myocardial infarction[b]	12
Sudden (possible arrhythmia)	6
Congestive heart failure	6
Repeat coronary artery bypass grafting[b]	4
Percutaneous transluminal coronary angioplasty[b]	3
Vascular	10 (15.9)
Cerebrovascular accident	4
Aortic disease	2
Other	4
Noncardiovascular	21 (33.3)
Malignancy	13
Other	8
Unknown	1 (1.6)
Total	63

[a] Numbers in parentheses are percentages. [b] This includes any death within 30 days of procedure or event.

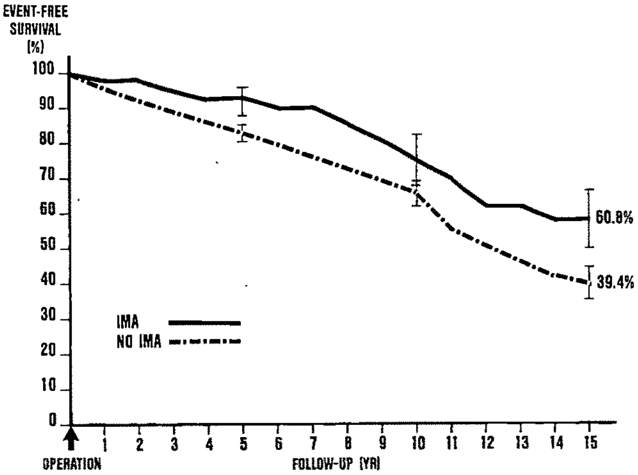

Fig 2. Event-free survival (± standard error) of patients in whom the internal mammary artery (IMA) was used and those in whom a vein (NO IMA) was used as the bypass conduit. There is a significantly (p = 0.02) improved status for the IMA group at 15 years of follow-up.

CABG or PTCA). Four of these 7 deaths occurred incident to 44 secondary and four tertiary coronary bypass procedures (8.3% operative mortality). The other 3 occurred incident to 44 PTCA procedures in 29 patients (6.8% mortality).

The event-free curve for all patients reveals an event-free status of 83.8% of patients at 5 years, 66.2% of patients at 10 years, and 43.2% of patients at 15 years after operation (see Fig 1).

Comparisons of survival and event-free survival in subsets of patients segregated according to age, sex, number of coronary artery bypass grafts constructed, and conduit used for coronary artery bypass are summarized in Table 4. There were no significant survival differences documented when patients were so grouped. However, there was marginally improved event-free survival (p = 0.11) when multiple bypass grafts were constructed and significantly improved event-free survival (p = 0.02) when an IMA was used (Fig 2).

Comment

It has been difficult to show a significant difference in late survival of patients with single-vessel coronary artery disease treated by CABG or medical treatment alone. This observation results, in part, from the fact that, in the absence of left ventricular aneurysm or ischemic cardiomyopathy, good survival has been documented in such patients regardless of therapy [4–11].

Two multicenter studies (the Veterans Administration Cooperative Study and the Coronary Artery Surgery Study) in which patients with single-vessel coronary artery disease were randomized to surgical versus medical treatment indicated that survival with medical therapy alone is better than that noted in previous reports, and that there are no significant differences in late morbidity

Table 4. Influence of Various Factors on Late Survival and Morbidity

			15-Year Incidence			
Factor	Category	No. of Patients	Survival (%)	p Value	Event Free[a] (%)	p Value
Age (yr)	32–54	134	79.2	0.25	43.6	0.85
	55–76	132	64.5		42.1	
Sex	Male	198	71.4	0.78	44.1	0.62
	Female	68	75.3		40.3	
No. of bypass grafts	Single	238	72.6	0.80	42.0	0.11
	Multiple[b]	28	76.5		58.7	
Bypass conduit	Internal mammary artery	39	78.6	0.31	60.8	0.02
	Vein	227	71.5		39.4	

[a] Events include acute myocardial infarction, repeat coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, and death. [b] Only 14-year data are available in this small group.

or survival between the two treatment groups [9, 11–16]. However, it should be noted that certain high-risk subgroups of patients were excluded from these studies. Also, one statistical difficulty in evaluating such data is the late "crossover" (reported to be as high as 4.7% per year) of patients from medical to surgical treatment groups [14]. The data of Proudfit and co-workers [17] showed that the slope of the survival curve of medically treated patients with single-vessel disease becomes steeper beyond 4 years of follow-up. In summary, however, these comparative studies have demonstrated no significant difference in morbidity and survival through 11 years of follow-up when comparing surgical versus medical treatment for single-vessel coronary artery disease.

Isolated LAD disease has been shown to be more lethal than other forms of single-vessel coronary artery disease [4, 17]. Survival data for patients receiving medical treatment of isolated LAD disease [1] reported during the interval of patient entry into the present series suggested that there is a higher 5-year mortality (20%) with medical treatment than was observed in the present series (4.5%).

In 1983, Proudfit and associates [17] presented a 15-year follow-up of medically treated patients who had single-vessel coronary artery disease and were suitable candidates for CABG. Although Proudfit and associates did not give specific data for patients with isolated LAD disease, the data did show that the 15-year survival for patients who had single-vessel disease and were judged to have been surgical candidates was 58%. Fifteen-year survival in one study is 72.7%. It should be cautioned, however, that different selection criteria and study methodologies were employed in these studies, making direct comparisons difficult.

None of the three large multicenter prospective randomized studies of medical versus surgical treatment for coronary artery disease have published an analysis of late follow-up in the subset of patients with isolated LAD disease [9–16, 18]. Okies and co-workers [19] reported 10-year survival of 81.1% among patients having single CABG (not necessarily single-vessel coronary artery disease) to the LAD. Also, Loop and associates [20] reported 10-year survival (emergency cases and operative deaths were excluded) of 90.3% among 772 surgically treated patients with isolated LAD disease. The 10-year survival in our series was 86.1%.

Improved long-term patency of IMA over saphenous vein grafts has been consistently confirmed by others, and the left IMA can almost always be used as a bypass graft to the LAD or its branches [6, 20, 21]. In general, published studies of overall experiences with CABG [19, 20] have been consistent in confirming better, although not necessarily significantly better, long-term survival when the IMA is used. Loop and associates [20] compared the long-term effectiveness of the IMA versus the saphenous vein as the bypass conduit in patients with isolated LAD disease. They found a 10-year survival (excluding operative deaths) of 93.4% and 88.0% with use of the IMA and the saphenous vein, respectively ($p = 0.05$). The data analyzed in the present report also show decreased late morbidity and improved survival when the IMA is used. However, the differences observed reach significance only when acute nonfatal events and mortality together (event-free status) are compared (see Table 4; Fig 2).

The consideration of CABG versus medical treatment for isolated LAD disease is perhaps a moot question at present. The current trend in the United States is toward coronary angioplasty in patients with isolated LAD disease seen with unstable or chronic stable angina. Surgeons less frequently see such patients unless there has been failure of either acute or repeated revascularization attempts by the cardiologist. Perhaps in the future most patients referred for CABG will be those in whom interventional treatment for acute ischemic episodes failed or those who have more recalcitrant disease.

Our series of patients were operated on before modern methods of intraoperative myocardial protection were used. The currently available anesthesia techniques, systems of cardiopulmonary bypass, cold cardioplegia, and sophisticated postoperative monitoring suggest the potential for even better results with CABG in patients with isolated LAD disease. Also, the superiority of the IMA over the saphenous vein is now more fully appreciated, and it is thought that the more frequent use of this vessel as a bypass conduit will also improve the long-term results. Nevertheless, we believe that a 15-year survival of 72.7% of patients operated on in the early 1970s (compared with a 15-year survival of 71.2% in an age-matched and sex-matched general population) substantiates the long-term effectiveness of CABG in patients with isolated LAD disease. Perhaps such late follow-up as reported here and from other institutions will supply a data pool with which results obtained by medial treatment alone or interventional techniques by cardiologists can be compared.

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Notice From the Southern Thoracic Surgical Association

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Phoenician Golf and Tennis Resort, Scottsdale, AZ, November 9–11, 1989. There will be a $155 registration fee for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 9, 1989. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1989, to Bradley M. Rodgers, MD, Program Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract submission form. These forms may be obtained from the Association's office or in this issue of *The Annals of Thoracic Surgery*. All slides used during the presentation must be 35 mm. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1989 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1989, and forwarded to Hooshang Bolooki, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601.

Gordon F. Murray, MD
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Chicago, IL 60601

Latissimus Dorsi Dynamic Cardiomyoplasty

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Department of Cardiovascular Surgery, Hopital Broussais, Paris, France, and Bakken Research Center, Maastricht, the Netherlands

Cardiomyoplasty is a new surgical technique that uses an electrostimulated skeletal muscle to reinforce or partially replace the heart muscle. Since the first clinical case performed in 1985, long-term beneficial cardiac effects of latissimus dorsi cardiomyoplasty have been documented in patients with various myocardial diseases (ischemic, neoplastic, dilated cardiomyopathy). In this article we describe the surgical technique that we have developed to biomechanically assist severe and irreversible ventricular failure.

(Ann Thorac Surg 1989;47:600–4)

Dynamic cardiomyoplasty involves the use of an electrically stimulated skeletal muscle wrapped around part of the heart to restore or augment ventricular contractility [1]. In our approach, a latissimus dorsi muscle flap (LDMF) is transferred through a window made in the chest by partial removal of the second rib, and is then used either to reinforce the entire heart or as a myocardial substitute to repair a large defect after removal of large ventricular aneurysms, cardiac tumors, or echinococcal cyst formations (Fig 1).

A sequential and progressive stimulation protocol is initiated 2 weeks postoperatively, allowing time for muscle flap recovery and adhesion formation between the muscle and epicardium. The muscle flap is electrostimulated in synchrony with ventricular systole, initially using single pulses and later using bursts of impulses [1–3]. The electronic device is composed of a Cardiomyostimulator (implantable pulse generator), as well as intramyocardial sensing and muscular pacing electrodes. The demonstration of electrical induction of fatigue resistance in skeletal muscle by metabolic myofibrillar transformation (glycolytic toward oxidative) is the basic principle of this biomechanical assist system [4, 5].

Material and Methods

Approach

Cardiomyoplasty can be performed using either the left or right LDMF, depending on the localization of the heart disease. Left cardiomyoplasty is most frequently used. There are two surgical options in performing a latissimus dorsi dynamic cardiomyoplasty. The first is via a single thoracic incision: by a lateral approach the LDMF is dissected, and then a thoracotomy through the fifth intercostal space allows fixation of the skeletal muscle over the heart. The second option is by means of two separate incisions, a lateral cutaneous approach to prepare the LDMF and subsequent median sternotomy. The second approach is preferred by our group, because the hemodynamic situation is more easily controlled, the muscle fixation over the heart is better performed, and the electronic device is placed far from the cutaneous dissection, a potential area of wound complications and bacterial contamination. Furthermore, sternotomy is necessary when associated cardiac procedures are planned using extracorporeal circulation.

Dissection and Transposition of the Latissimus Dorsi Muscle Flap

With the patient in the lateral decubitus position, the cutaneous incision is performed at the level of the lateral border of the scapula, from the axillary region toward the intersection between the iliac crest and paravertebral muscles. The mean length of incision in adults is 33 cm (Fig 2A). The latissimus dorsi muscle (LDM) is dissected free from the iliac crest, vertebra, inferior scapular angle, and ninth to twelfth rib attachments. Particular attention is necessary in identifying the anterior muscular insertions, in continuity with the obliquus externus abdominis. Dissection of the LDMF must be performed carefully, mainly with scissors; electrocautery, if needed, is used with great care and with low intensity to minimize injury to the vascular supply. Latissimus dorsi muscle flap hemostasis is completed when the collateral blood vessels arising from intercostal arteries are divided, during dissection of the distal part of the flap. After the flap has been freed of its distal insertions, the superior neurovascular bundle is identified and carefully preserved.

A 5-cm segment of the anterior portion of the second rib including periosteum is then resected to allow transposition of the LDMF into the thorax. To perform chronic muscular stimulation, two juxtaneural pacing electrodes (Medtronic SP 5528; Maastricht, the Netherlands) are implanted in the proximal portion of the LDMF. The cathode is placed in close proximity to the course of the main nerve branches to produce a diffuse stimulation of the flap. The anode is implanted transversely into the muscle, 6 to 8 cm distal to the cathode (Fig 2B). The middle and distal parts of the LDMF, which will be grafted over the heart, are free of electrode implantation.

Electrophysiological tests (threshold, impedance) are performed. To perform these tests, it is important to anesthetize the patient without curariform drugs. The LDMF and attached leads are then transposed into the left

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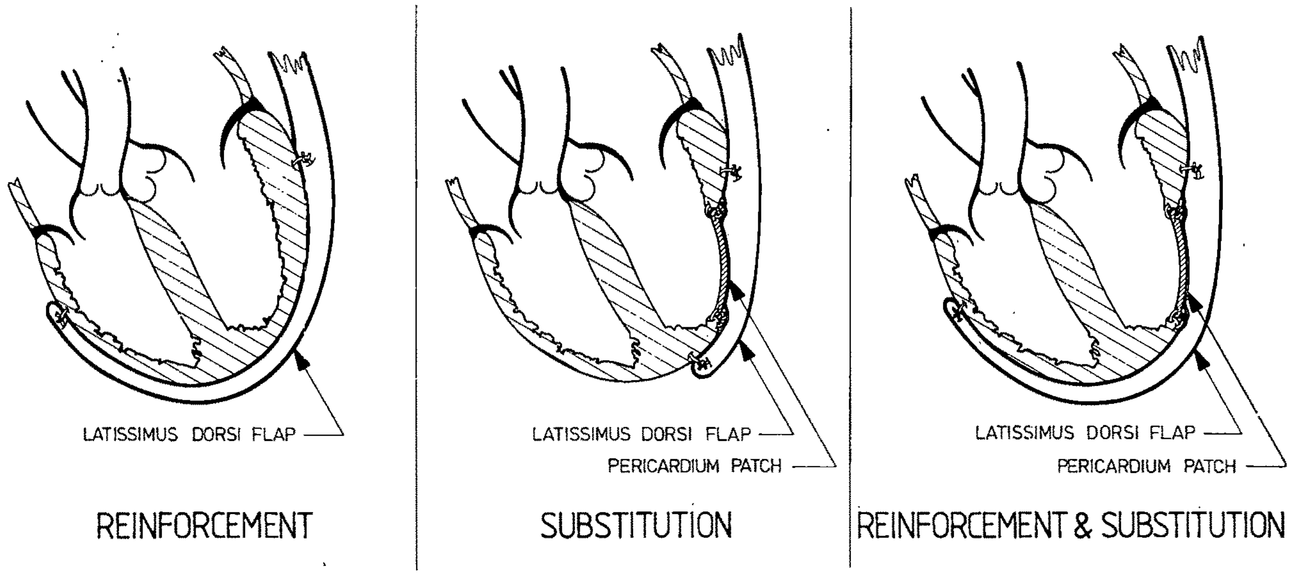


Fig 1. Different approaches for latissimus dorsi dynamic cardiomyoplasty.

pleural cavity. A pleural drain is placed and the muscle is fixed with four interrupted sutures to the intercostal muscles at the level of the second rib resection. This is performed to close the pleural cavity and to prevent traction of the stimulated LDMF over its neurovascular pedicle. To avoid left arm movement during electrostimulation, the latissimus dorsi humeral tendon is then severed at its most proximal part. Three subcutaneous drains are placed between the cutaneous flaps and the chest wall. The cutaneous flaps are then secured to the thoracic wall with interrupted absorbable suture and the wound is closed. This portion of the cardiomyoplasty procedure requires approximately 110 to 130 minutes.

Cardiomyoplasty

The patient is then placed in the supine position and the heart is exposed through a median sternotomy incision. Access to the LDMF and pacing leads is obtained with a long incision in the left pleura. Depending on the cardiac lesion, one of the following procedures can be considered.

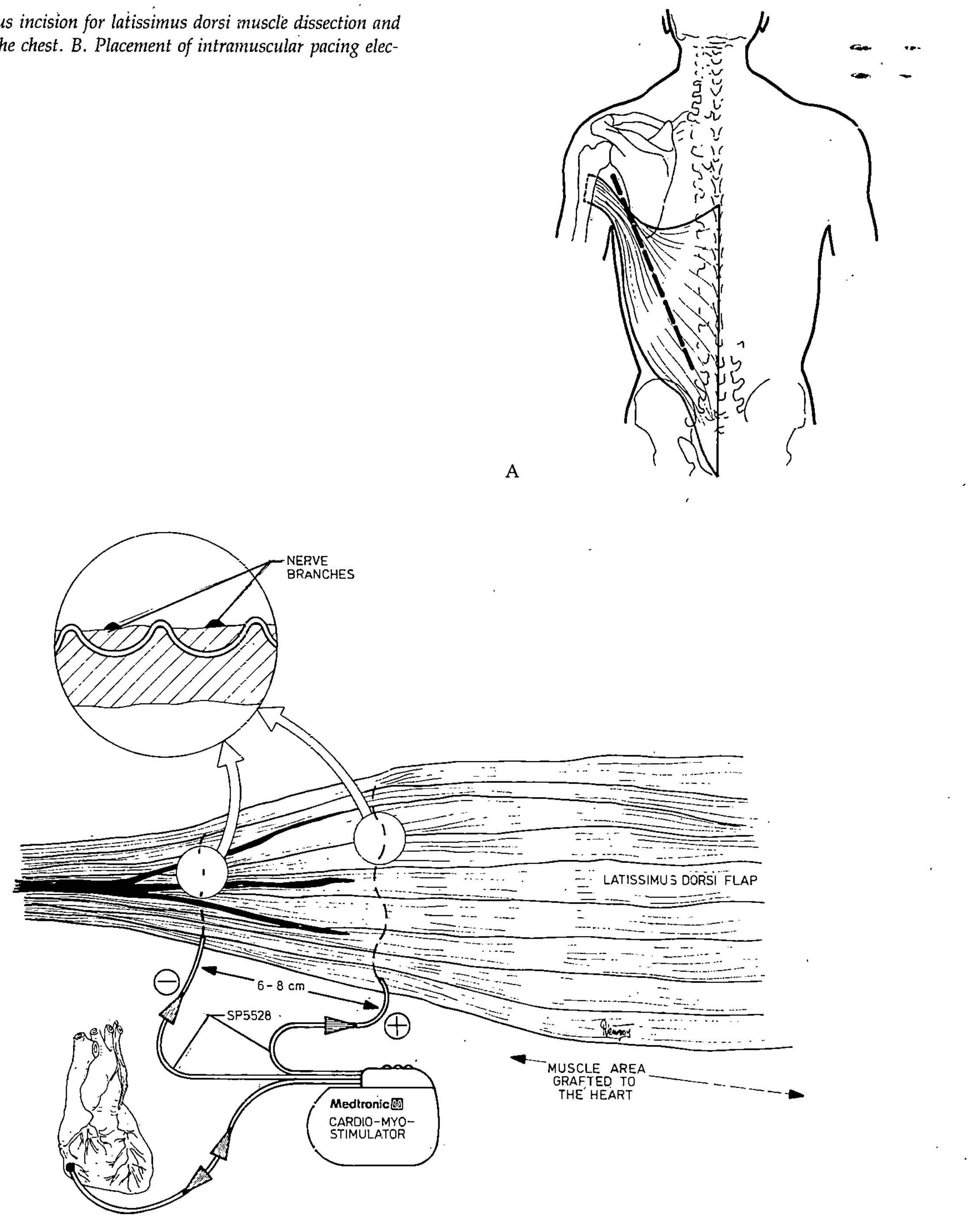
VENTRICULAR REINFORCEMENT. To perform a ventricular wrap with the LDMF, cardiopulmonary bypass is generally not required. Nevertheless, it should always be available on standby. The region of the LDMF with the best contractility (the middle segment) will be in contact with the most dysfunctional area of the ventricular wall. The deep fascia of the LDM is placed in contact with the epicardial surface of the heart. It is preferable to orient the muscle fibers perpendicularly to the ventricular septum, wrapping the heart in a clockwise manner, beginning on the diaphragmatic ventricular wall (Fig 3A).

The heart is lifted and four to six interrupted myocardial sutures (3-0 or 4-0 braided polyester) are placed from the posterior atrioventricular junction, longitudinally in the intercoronary spaces, to the spinal border of the flap (Fig 3B). After the LDMF is secured behind the heart, two intramyocardial sensing leads (Medtronic SP 5548) are implanted into the left or right ventricle wall. The R-wave amplitude is measured and the lead with the best value is connected to the sensing channel of the cardiomyostimulator (Medtronic SP 1005). The muscle stimulator will be triggered by the QRS complex. The other intramyocardial lead is capped and left as a spare electrode. The wrap is then completed, placing sutures between the lateral and anterior walls of the right and left ventricles and the LDMF (Fig 3C). A single additional suture must be placed between the middle part of the LDMF and the lateral wall of the left ventricle to promote muscle adhesion to this area (Fig 3A, *arrow*). If, during fixation of the LDMF behind the heart, severe hemodynamic dysfunction occurs, suture of the flap over the diaphragmatic ventricular wall can be abandoned. In these cases, it is preferable to delay the LDMF electrostimulation an additional week to allow sufficient adhesion formation between the LDM and heart. In cases in which extreme heart dilation does not allow complete muscle wrapping because of insufficient LDM mass, the anterior wall of the right ventricle can be left without muscle covering or can be covered by a piece of autologous pericardium. This pericardial patch must be attached in continuity with the LDMF and placed anteriorly on the right ventricle (Fig 3D). In this situation, one could hypothesize that a second complementary cardiomyoplasty using the right LDM might be performed several months later.

A pocket for the Cardiomyostimulator is then fashioned beneath the right rectus abdominis muscle. Muscle and cardiac leads are tunneled to the pocket and coupled with the stimulator. Left pleural and pericardial drains are exteriorized at the left side of the epigastrium, far from the electronic device. The pericardium is left open and the sternotomy is then closed.

VENTRICULAR SUBSTITUTION. The LDM dissection and median sternotomy are performed as described for ventricular reinforcement. The patient is placed on cardiopulmo-

Fig 2. A. Cutaneous incision for latissimus dorsi muscle dissection and transposition into the chest. B. Placement of intramuscular pacing electrodes.



nary bypass and resection of the ventricular pathology is performed.

In the substitution approach there are two steps: first, a patching procedure to close the ventricular defect with a piece of autologous pericardium sutured to endocardium and myocardium using a running 4-0 suture, and second, the wrapping of the ventricular surface and the pericardial patch with the LDMF. The pericardial "neoendocardium," which possesses nonthrombogenic characteristics, facilitates hemostatic closure of the ventricular defect and lessens the possibility of a latissimus dorsi interfascicular hematoma after the ventricular reconstruction [3, 6, 7]. We prefer to fix intraoperatively, before implantation, the pericardial patch with a glutaraldehyde solution (0.62%; minimum immersion time, ten minutes) [8]. Our clinical experience has shown that this treatment allows sufficient collagen cross-linking to ensure pericardial stability.

In some cases, the endocardium remaining after aneurysmectomy is sufficient for ventricular closure. In these situations, the LDMF is directly attached after hemostatic

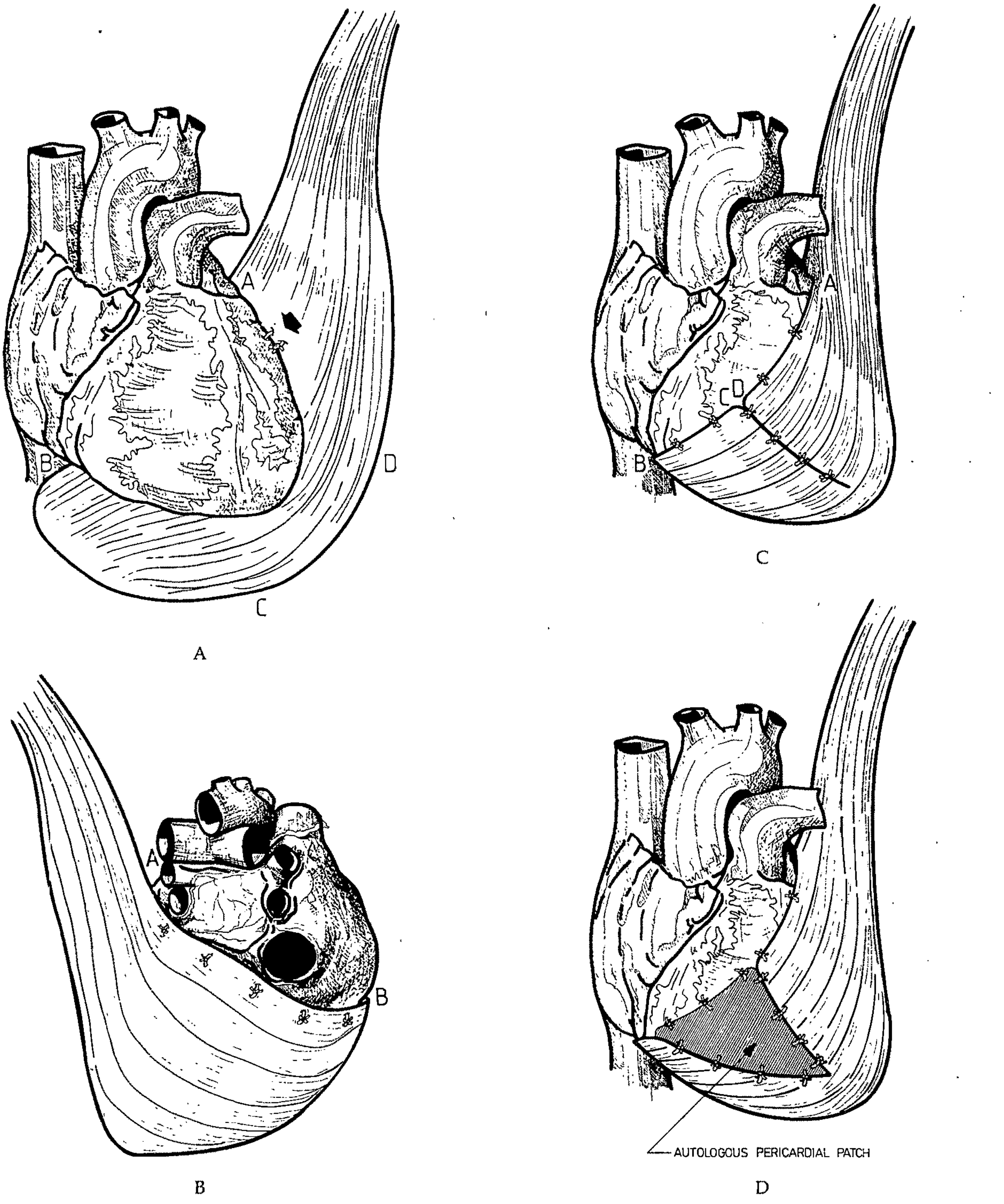


Fig 3. A. The latissimus dorsi muscle flap in the thoracic cavity is positioned behind the heart. B. Posterior view of the heart. The muscle is first fixed to the posterior atrioventricular region. C. Muscle wrapped and sutured onto the anterior wall of the ventricles in a clockwise manner. D. Wrapping completed with autologous pericardium, to be used in cases of extreme cardiac dilation.

closure of the defect. Sensing electrodes and the Cardiomyostimulator are implanted as described for ventricular reinforcement.

Comment

The cardiomyoplasty procedure is intended for use in patients with chronic low cardiac output states refractory to pharmacological support, secondary to ischemic, neoplastic, infectious (chagasic, viral), or congenital causes, before end-stage cardiac dysfunction. Results of experimental work allowed us to progress to the first clinical application of this technique in humans in January 1985 [2]. At present, our successful clinical experience (patients discharged from the hospital with improved ventricular function) involves 10 patients with severe preoperative cardiac dysfunction (New York Heart Association class III and IV), in which the reinforcement (6 cases) or substitution approach (4 cases) was performed. This early experience (mean follow-up, 15 months) demonstrates that dynamic cardiomyoplasty was clinically effective, after the institution of electrical myostimulation. Postoperative technetium 99m heart scan, ultrasonic Doppler echocardiography, and hemodynamic studies reveal improvement in ventricular contractility and limitation of heart dilation with no tendency of the LDMF to constrict the heart. These patients are currently in functional class I (2 patients) and II (8 patients) [1, 9].

Dynamic cardiomyoplasty, by improving ventricular contraction and limiting cardiac dilation [10], can therefore be a positive factor to enhance cardiac performance and to prolong and improve the quality of life of patients suffering from severe chronic myocardial dysfunction [9, 11].

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Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hyatt-Regency, Dallas/Fort Worth Airport, Dallas TX, on February 4, 1990. The closing date for registration is August 1, 1989.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Mitral Valve Fibroelastoma

Michael E. Gorton, MD, and Hooshang Soltanzadeh, MD

Department of Surgery, Iowa Methodist Medical Center, Des Moines, Iowa

Papillary fibroelastomas are rare benign tumors of the heart with predisposition for cardiac valvular involvement that were traditionally incidental findings at autopsy. Echocardiography now is allowing clinicians to diagnose these tumors in living patients. We reviewed the literature and, to our knowledge, are reporting the fifth documented case of a mitral valve papillary fibroelastoma in a living patient. Our patient was seen with bilateral transient ischemic attacks and was found to have a mitral valve tumor by two-dimensional echocardiography and cardiac catheterization. The tumor involved the entire mitral valve and subvalvular structures. The patient's valve was replaced with a bioprosthesis, and she remains free from symptoms.

(Ann Thorac Surg 1989;47:605–7)

The patient is a 77-year-old woman with a history of bilateral transient ischemic attacks. She had transient right arm weakness in September 1985. She then had transient left hand weakness and memory loss in March 1986. Six days before hospitalization she had recurrent left hand weakness that slowly resolved.

The patient's past medical history included hypertension and polycythemia vera, but she had a normal platelet count and hemoglobin level during each of the transient ischemic attacks. Her medications included calcium channel blocker, digitalis, and aspirin.

Examination on admission revealed good carotid pulses without bruits. The cardiac examination revealed regular rate and rhythm with normal first and second heart sounds. No murmurs or extra heart sounds were heard. She had no neurological deficits.

A carotid duplex scan showed normal carotid arteries. A Holter monitor revealed a transient second degree atrioventricular block but no other notable findings. On two-dimensional echocardiogram she was found to have a movable mass lesion attached to the mitral valve (Fig 1). She underwent cardiac catheterization, which revealed a negative filling defect on the anterior leaflet of the mitral valve consistent with a pedunculated valvular tumor. She had normal coronary artery anatomy and good left ventricular function.

At exploration, she was noted to have multiple frond-like tumors projecting from the annulus of the mitral valve, both leaflets, the chordae tendineae, and the papillary muscles (Fig 2). The tumors ranged from 2 mm to 2 cm in diameter. Frozen section biopsy specimens resembled a myxoma. Permanent sections revealed a dense core of connective tissue surrounded by endothelial cells consistent with papillary fibroelastoma (Fig 3).

Complete removal of the tumor required excision of the mitral valve, chordae tendineae, and papillary muscle. A no. 27 Carpentier-Edwards bioprosthesis was inserted. The patient had a benign postoperative convalescence. She remains free from symptoms and is neurologically intact at 9 months of follow-up.

Comment

A papillary fibroelastoma is a rare tumor of the heart with predilection for valvular involvement. These tumors comprise 7% to 8% of heart tumors in autopsy series [1], but only four such tumors that involve the mitral valve have been reported in living patients (Table 1). Shub and colleagues [2] in 1981 were the first to diagnose a mitral valve papillary fibroelastoma in an asymptomatic patient undergoing evaluation for a heart murmur. They successfully excised the tumor and inserted a prosthetic valve. A 35-year-old patient with multiple transient neurological deficits without clinical cardiac findings underwent valve replacement by Fowles and co-workers [3] after a fibroelastoma was noted on his mitral valve by two-dimensional echocardiogram. Marvasti and associates [4] treated a similar patient with simple tumor excision. Topol and co-workers [5] used transesophageal echocardiography to guide a valve-sparing excision of a mitral valve fibroelastoma from a 27-year-old patient who was seen with a completed stroke.

Our patient was seen with bilateral transient ischemic attacks. Work-up was negative except for a mitral valve tumor noted on two-dimensional echocardiography. The tumor involved the entire valve and subvalvular structures, which necessitated their excision and replacement with a bioprosthetic valve. The patient remains symptom-free at 9 months of follow-up.

The nomenclature in the literature is confusing because many names (fibroma, cardiac papilloma, valvular papilloma, papillary endocardial fibroma, myxoma, myxofibroma, papillary fibroma, fibroelastic hamartoma, fibroangiomyxoma, papillary myxoma, hemangioelastomyxoma, papillary excrescence, giant Lamble excrescence, and papillary endocardial tumor) have been used to describe this tumor [6, 7]. Papillary elastofibroma is now the accepted term and very accurately describes its gross and histological appearance.

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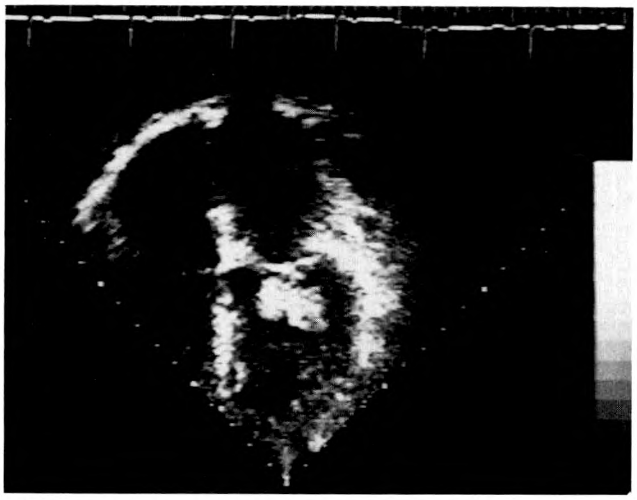

Fig 1. Two-dimensional echocardiogram illustrating a pedunculated tumor attached to the anterior leaflet of the mitral valve.

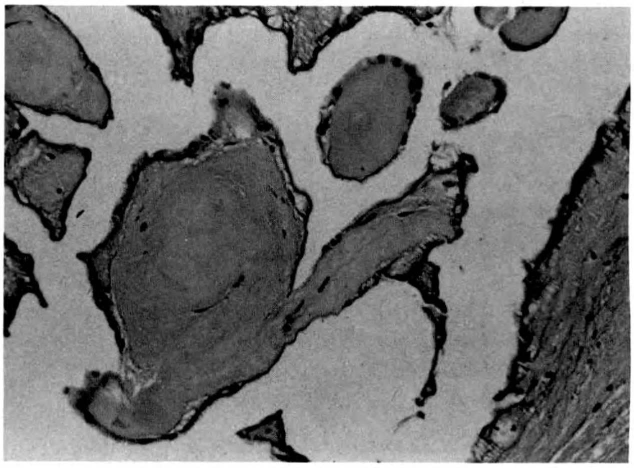

Fig 3. High-power photomicrograph of this patient's papillary fibroelastoma, stained with hematoxylin and eosin. Note the dense core of connective tissue surrounded by endothelial cells.

Papillary fibroelastomas are related to myxomas but are quite distinct. They are benign tumors with multiple papillary fronds resembling a sea anemone, and most frequently arise from cardiac valves, although they may arise from virtually any endocardial surface [8]. The distribution of papillary fibroelastomas found in a 42-patient autopsy series was as follows: aortic valve, 15; tricuspid valve, 9; pulmonary valve, 8; mitral valve, 7; right atrium, 2; right ventricle, 2; left ventricular septum, 1; left atrium, 1. They have a central core of dense connective tissue lined by sometimes hyperplastic endocardial tissue and have a resemblance to normal chordae tendineae [4]. Some authors believe that they are hamartomas, whereas others believe that they are true neoplastic growths perhaps related to chronic trauma [4].

Myxomas, on the other hand, arise from a reversion of fibroblastic cells to embryonic growth and have low-grade malignant potential. They consist of loose, poorly cellular myxomatous tissue and are usually solitary lesions arising from a pedicle near the fossa ovalis.

The mechanism behind systemic embolization from a papillary fibroelastoma is not known exactly, but the most logical explanation is that offered by Topol and associates [5], who theorized the tumor was a nidus for platelet and fibrin aggregation that subsequently embolized. We propose that symptomatic patients without prohibitive risk factors should undergo surgical excision of the lesion and valve replacement if necessary.

In summary, cardiac papillary fibroelastomas are capable of producing systemic embolization and now should be included in the differential diagnosis of transient ischemic attack and stroke. Similar to atrial myxomas and mural thrombi, they are easily diagnosed by two-dimensional echocardiography. Patients with papillary

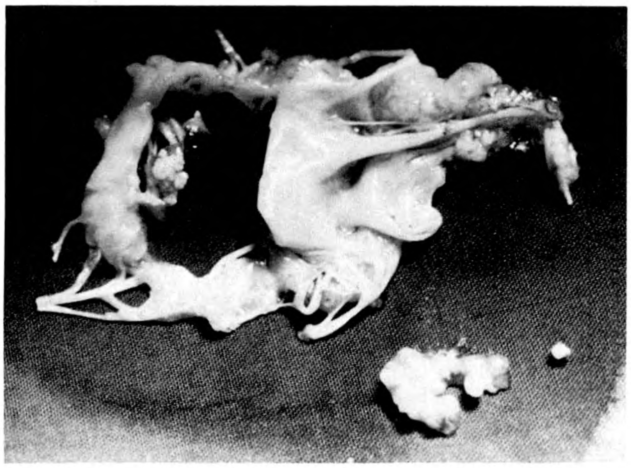

Fig 2. Intraoperative view of the mitral valve and subvalvular structures involved by tumor. Note the separate pieces of tumor in the lower right-hand corner that were loosely attached to the valve leaflets.

Table 1. Mitral Valve Papillary Fibroelastomas Detected by Two-Dimensional Echocardiography in Living Patients Who Have Undergone Successful Resection and/or Valve Replacement

Year	Study	Location	Presenting Symptoms
1981	Shub et al [2]	Mayo Clinic, Rochester, MN	Asymptomatic
1981	Fowles et al [3]	Stanford University, Stanford, CA	TIA
1983	Marvasti et al [4]	Upstate Medical Center, Syracuse, NY	TIA
1986	Topol et al [5]	Johns Hopkins University, Baltimore, MD	Stroke
1989	Gorton et al [present study]	Iowa Methodist Medical Center, Des Moines, IA	TIA

TIA = transient ischemic attack.

fibroelastomas have normal auscultatory cardiac examinations, unlike patients with myxomas, which usually produce a tumor "flop". The frequency of valve tumors discredits reports that two-dimensional echocardiography is unnecessary in patients with transient ischemic attacks or stroke who have no clinical or electrocardiographic evidence of heart disease.

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Percutaneous Cardiopulmonary Bypass for the Treatment of Hypothermic Circulatory Collapse

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George J. Magovern, MD, and Joseph C. Young, MD

Department of Thoracic and Cardiovascular Surgery, Deborah Heart and Lung Center, Browns Mills, New Jersey, and Divisions of Cardiothoracic Surgery and General Surgery, Department of Surgery, Allegheny General Hospital, Pittsburgh, Pennsylvania

Environmentally induced hypothermia has a very high mortality. Cardiopulmonary bypass affords the best chance of survival from hypothermia but can be time-consuming to institute. We have utilized percutaneous cardiopulmonary bypass with recently developed bypass catheters to resuscitate a patient with profound hypothermia complicated by circulatory collapse. Percutaneous cardiopulmonary bypass appears to be the treatment of choice for profound hypothermia.

(Ann Thorac Surg 1989;47:608–11)

Severe hypothermia secondary to environmental exposure has an extremely high mortality rate [1–4]. Cardiopulmonary bypass (CPB) with active rewarming has achieved the best salvage rates of the numerous rewarming methods used in this situation [5]. Cardiopulmonary bypass is an attractive technique because it provides circulatory support in addition to rapid, efficient core rewarming [1, 3].

Widespread use of CPB in this setting has been hampered by several factors. Traditional methods of cardiac bypass usually require surgical exposure of the great vessels, which can be time-consuming and difficult, especially in the emergency environment. Femoral cannulation has been advocated for emergent situations. This technique is less demanding, but still requires surgical exposure of the femoral vessels. In addition, full cardiopulmonary support is not consistently obtainable via the femoral route because venous drainage can be inadequate through existing femoral cannulas.

We have developed a new technique for initiation of CPB using novel percutaneous femoral venous and arterial cannulas (LPEBS, Cook Critical Care, Bloomington, IN) designed and developed by one of us (G.W.L.) that greatly facilitates institution of cardiopulmonary bypass. We report here a patient with profound hypothermic circulatory collapse treated successfully with percutaneously initiated cardiopulmonary bypass.

A morbidly obese (height, 1.63 m; weight, 120 kg) 60-year-old woman, last seen 36 hours previously, was found by family members in an unheated apartment (ambient temperature, 1°C). On arrival to an outlying emergency department, she was unresponsive and in circulatory arrest with a rectal temperature of 26°C. Initial resuscitation included endotracheal intubation, cardiopulmonary resuscitation, and infusion of dopamine at a rate of 35 μg/kg/min.

On arrival to our institution, the patient had bilateral fixed and dilated pupils (Glasgow coma score = 3). She was in circulatory collapse with an unstable cardiac rhythm alternating between a junctional rhythm at a rate of 50 beats per minute and an idioventricular rhythm at a rate of 40 beats per minute. Cardiogenic shock persisted despite pressor support. Her core rectal temperature was 24°C.

She was taken immediately to the operating suite, placed on cardiopulmonary bypass, and actively rewarmed using a bubble oxygenator with a centrifugal pump. Vascular access was accomplished by using percutaneous bypass cannulas inserted into the femoral artery and vein utilizing a percutaneous Seldinger technique. After insertion of the arterial and venous cannulas, the patient was anticoagulated with 30,000 units of intravenous heparin and was given 1 g of methylprednisolone intravenously. Total elapsed time from arrival in the emergency department to institution of CPB was less than 20 minutes.

The patient was maintained on CPB with flow rates of 2 to 4 L/min for approximately 90 minutes, during which her core temperature rose to 37°C. With rewarming, her cardiac rhythm changed to atrial fibrillation at a rate of approximately 150 beats per minute. She was successfully cardioverted after her core temperature reached 34°C.

After termination of cardiopulmonary bypass, the catheters were removed using an open technique with suture repair of the arteriotomy and venotomy. The heparin was reversed with protamine.

The patient's postoperative course was uncomplicated. She was weaned from all pressors within 48 hours and had regained normal neurological function within 72 hours. A workup failed to reveal any cause for her hypothermia other than lack of heating in her apartment. She was discharged 7 days after admission.

Percutaneous Bypass Cannulas

The venous cannula, with stylet in position, is a smooth 30F heparin-coated cannula designed to be introduced

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Address reprint requests to Dr Laub, Deborah Heart and Lung Center, Browns Mills, NJ 08015.

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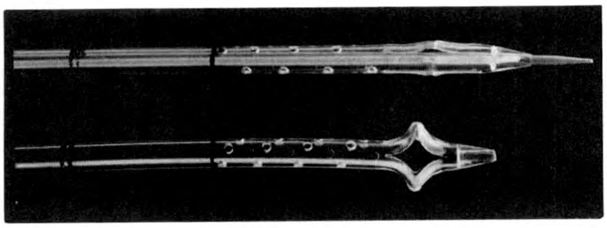

Fig 1. Venous cannula with stylet inserted (top) and removed (bottom). Note expanding basket near tip of cannula.

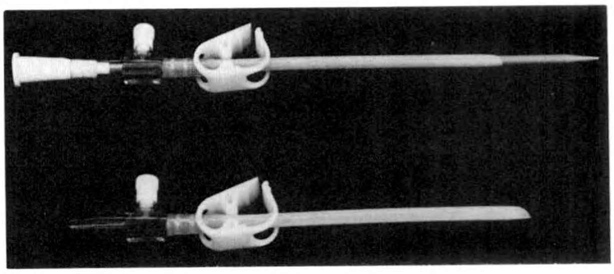

Fig 2. Arterial cannula with stylet inserted (top) and removed (bottom).

percutaneously over a guidewire. Once the cannula has been advanced into position over the guidewire, the stylet is removed, causing a basket near the end of the cannula to expand (Fig 1). Blood flows into the cannula from the sideholes and basket region, which, in addition, prevents the vascular space from collapsing around the catheter and impeding blood flow.

The arterial cannula is a 20F kink-resistant tube designed to be introduced into the femoral artery over a guidewire (Fig 2). Once both cannulas have been introduced, the patient is ready for cardiopulmonary bypass (Fig 3).

Comment

The estimated mortality for profound hypothermia is 30% to 80% [1–4]. Most patients die of ventricular dysrhythmias or circulatory collapse [2, 5–7]. Ventricular dysrhythmias, including asystole, are commonly triggered by external means such as insertion of a Swan-Ganz catheter, intubation, or moving the patient [7]. Circulatory collapse is a result of two factors: increased vascular resistance and depressed myocardial function. Autonomic-induced core and cutaneous vasoconstriction can markedly decrease tissue perfusion and increase afterload. Myocardial function, already depressed by severe hypothermia, is worsened by this increase in afterload.

In an attempt to restore normothermic conditions, several strategies have been proposed. Passive or external rewarming was one of the first techniques used and has the advantage of being universally available and simple to institute [1]. However, passive rewarming is associated with "rewarming shock." As cutaneous rewarming occurs, the peripheral vascular resistance falls more rapidly than core rewarming is accomplished; hence, myocardial dysfunction continues. As a result of the vasodilation and continued myocardial dysfunction, hypotension ensues. In addition, external rewarming causes an increase in the metabolic needs of the rewarmed tissue without a concomitant increase in tissue perfusion [1]. Active or inter-

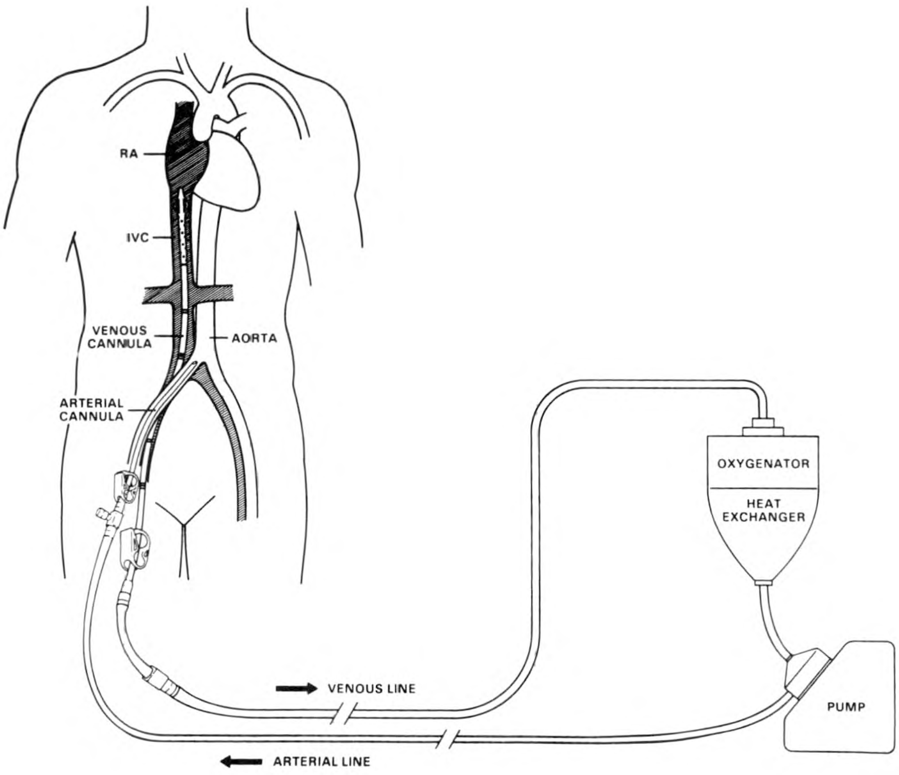

Fig 3. Percutaneous femoral to femoral bypass system for cardiac support and rewarming. Note location of venous cannula at junction of right atrium (RA) and inferior vena cava (IVC).

Table 1. Review of Survival of Profound Hypothermia Treated With Cardiopulmonary Bypass

Author	No. of Patients	Temperature (°C)	No. Survived	% Survived
Kugelberg et al [8]	1	21	1	100
Davies et al [9]	1	34	1	100
Fell et al [10]	1	29	1	100
Towne et al [11]	1	25	1	100
Truscott et al [7]	1	22	1	100
Wickstrom et al [2]	2	25, 20	1	50
Dorsey [12]	1	26	1	100
Althaus et al [3]	2	19, 24	2	100
Splittgerber et al [5]	6	22, 21, 21, 21, 23, 24	3	50
Maresca and Vasko [13]	2	25, 24	2	100

Fig 4. Photograph of the patient before discharge. As can be seen by the size of the patient, formal surgical placement of the arterial and venous cannulas could have been quite time-consuming.

nal rewarming methods have the advantage of allowing core temperature to rise with return of myocardial function as vasodilation occurs.

Active rewarming using cardiopulmonary bypass has been reported to provide excellent results (Table 1). This form of rewarming has the advantage of providing circulatory support during the rewarming phase. This is particularly important in patients with profound hypothermia complicated by circulatory collapse. The cumulative mortality in patients treated with this modality is 22%, well below the reported mortality using other techniques.

Table 2. Review of Techniques and Procedures of Cardiopulmonary Bypass

Author	Type of Bypass	Time to CPB[a]	Time on CPB[b]
Kugelberg et al [8]	femoral–femoral	120	72
Davies et al [9]	femoral–femoral	70	70
Fell et al [10]	atrial–aortic	390	40
Towne et al [11]	femoral–femoral	85	45
Truscott et al [7]	femoral–femoral	60	93
Wickstrom et al [2]	femoral–femoral	60	40
Dorsey [12]	femoral–femoral	90	30
Althaus et al [3]	femoral–femoral	140	20
Splittgerber et al [5]	femoral–femoral	168	70
Maresca and Vasko [13]	atrial–aortic and femoral–femoral	NA	135

[a] Time, in minutes, from arrival to institution of CPB; average given for multiple patients. [b] Time, in minutes, while on CPB; average given for multiple patients.

CPB = cardiopulmonary bypass; NA = not available.

As in our experience, most investigators use extracorporeal femoral to femoral bypass to accomplish rewarming (Table 2). Direct cannulation of the femoral vessels can be time-consuming. Percutaneous insertion obviates the surgical exposure required and allows more rapid institution of bypass.

Recently, Phillips and colleagues [14] have demonstrated the feasibility of percutaneous initiation of partial cardiopulmonary bypass for cardiogenic shock. The cannulas we used allowed higher flow rates to be attained, while preserving the speed of percutaneous insertion.

In the literature, the average time of institution of cardiopulmonary bypass was 134 minutes; the fastest time reported was 60 minutes (Table 2). In the patient presented in this report, cardiopulmonary bypass was established via percutaneous means within 20 minutes of arrival to the hospital. Surgical vascular access in this obese patient (Fig 4) would have been formidable and time-consuming. Time frame can be critical in the treatment of profound hypothermia complicated by circulatory collapse.

In conclusion, a novel percutaneous bypass cannula set allowed rapid percutaneous initiation of cardiopulmonary bypass for essentially full cardiac support and active rewarming in this patient. Percutaneous cardiopulmonary bypass with active rewarming appears to be the treatment of choice for hypothermic circulatory collapse.

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Traumatic Rupture of the Pulmonary Artery

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Traumatic rupture of the main pulmonary artery in a surviving patient is very rare. The case history of a 37-year-old man who sustained blunt chest trauma in a motor vehicle accident is presented. A persistent, bloody right pleural effusion led to the diagnosis of a ruptured right main pulmonary artery, which was surgically repaired using cardiopulmonary bypass. Points of diagnostic interest and therapeutic decision making are discussed.

(Ann Thorac Surg 1989;47:612–3)

Blunt chest trauma can be associated with life-threatening thoracic injuries such as tears of the thoracic aorta and arch vessels [1]. Chamber ruptures of the heart have also been reported [2, 3]. Reports of isolated injury to the main pulmonary arteries are common in penetrating chest trauma, but traumatic tears of the main pulmonary arteries due to blunt chest trauma in surviving patients are rare.

Most cases of traumatic rupture of the main pulmonary arteries are accompanied by concomitant injuries to other mediastinal or hilar structures such as the trachea or mainstem bronchi [4]. Our literature search has failed to reveal a case of blunt chest trauma with isolated main pulmonary artery injury in a surviving patient. Here, we report the case of a surviving patient who sustained severe blunt chest trauma in an automobile accident, which resulted in a large laceration of his right main pulmonary artery with no other clinically significant intrathoracic or mediastinal injuries. Repair was accomplished through a midline sternotomy using cardiopulmonary bypass.

A 37-year-old man was admitted to the emergency room after sustaining a rapid deceleration injury in an automobile accident. The patient sustained a closed head injury, blunt injuries to the chest, and injuries to his lower face, left knee, and left wrist. On initial examination he was found to be combative and agitated. Because of signs of respiratory distress he was intubated and paralyzed. His systolic blood pressure was 40 mm Hg. Large-bore central lines were inserted and his blood pressure was supported with lactated Ringer's solution and type-specific blood. A chest roentgenogram showed a widened mediastinum, a right lung contusion, and a fractured right fifth rib. There was no pneumothorax or pleural effusion. A thoracic aortogram was negative for aortic injury, and a computed tomographic scan of the head and abdomen was normal. Eventually the patient became more alert and cooperative, and his behavior more appropriate. The patient was admitted to the Shock-Trauma Unit with stable vital signs for further observation. Over the next 24 hours, his pulmonary function improved and he was extubated.

Over the next two days the patient accumulated a right pleural effusion. Thoracentesis on his second hospital day revealed 900 mL of bloody fluid. The effusion recurred and the patient started to complain of severe right pleuritic chest pain. A right chest tube was placed and another 500 mL of bloody fluid was drained. Thoracic surgery consultation was obtained, after which a pulmonary angiogram was performed. This study revealed a false aneurysm of the right main pulmonary artery, just at the takeoff of the right upper lobe branch (Fig 1).

The patient was taken to the operating room, where his right main pulmonary artery was exposed through a midline sternotomy, using cardiopulmonary bypass to decompress the pulmonary arterial system during the repair. The patient had no contraindications to heparinization. The false aneurysm was approached through the aortocaval recess and posterior pericardium. A spiral tear around one half of the circumference of the right main pulmonary artery was repaired by reapproximation using a running simple suture of 5-0 polypropylene. The patient was easily weaned from cardiopulmonary bypass and required no pharmacological support. His postoperative course was uncomplicated, and he was discharged on his 16th postoperative day after a slow but uneventful recovery.

Comment

An extensive literature search indicates that one of the rarest forms of pulmonary artery pseudoaneurysm is that due to blunt chest trauma. Hanline [5] reported a case of a 27-year-old man who sustained multiple blunt injuries in an automobile accident. That patient was found to have bilateral torn hilar vessels at autopsy, without other hilar or mediastinal injuries. Rupture of the main pulmonary arteries in autopsy series performed on patients sustaining blunt chest trauma is rare [6]. Dillon and associates [7] reported a case of blunt chest trauma in a 50-year-old man who sustained a tear at the takeoff of the right upper lobe pulmonary artery with no associated airway or other vascular trauma. Repair was approached through a right thoracotomy and resulted in a right pneumonectomy. The

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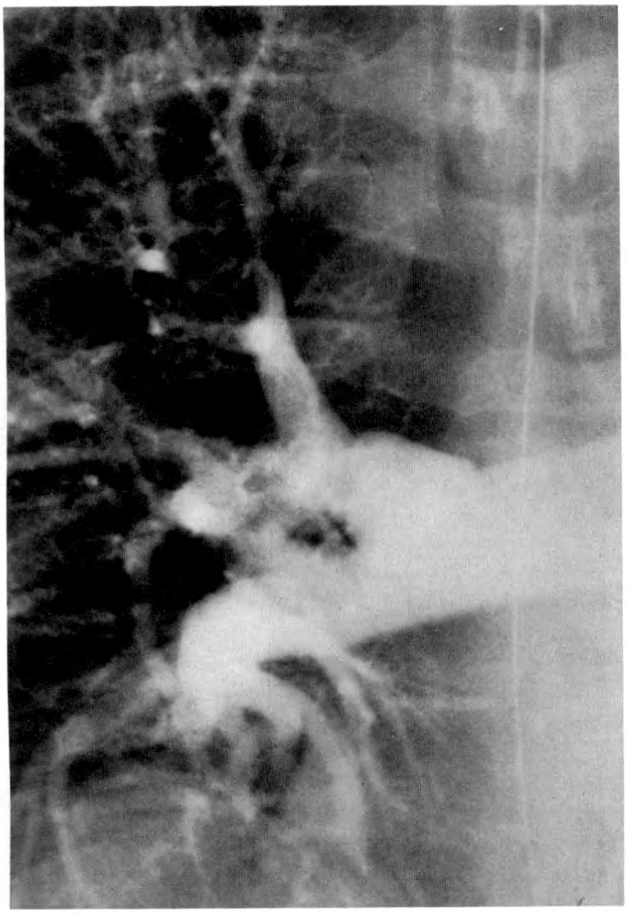

Fig 1. Pulmonary arteriogram showing a false aneurysm at the take-off of the right upper lobe branch.

patient eventually died on the third postoperative day of pulmonary emboli to his remaining lung.

In our patient, it was felt that a right thoracotomy approach would carry a higher risk of pneumonectomy compared with a central approach using cardiopulmonary bypass. Because there were no contraindications to heparinization, repair was accomplished using a midline sternotomy and cardiopulmonary bypass.

This report emphasizes the following diagnostic points. First, rupture of the pulmonary artery by blunt chest trauma need not be accompanied by tracheal or bronchial tears or any other major mediastinal or thoracic injuries. Second, rupture of the pulmonary artery must be suspected in blunt chest trauma in the face of a widened mediastinum and a negative thoracic aortogram, especially in the presence of a persistent or recurrent hemothorax. This may be investigated by pulmonary angiography or a perfusion lung scan.

The use of cardiopulmonary bypass in this patient afforded a less threatening route of access to the repair of the pulmonary artery. Using this technique, the pulmonary system is decompressed and is easy to manage. In the standard posterolateral thoracotomy, if control of the pulmonary artery is lost then a pneumonectomy must generally be performed to avert a hemorrhagic catastrophe.

In conclusion, the triad of a widened mediastinum and a negative thoracic aortogram, continued bloody pleural effusion, and persistent pleuritic pain should alert the surgeon to the possibility of a pulmonary artery injury, and a pulmonary angiogram should be considered. If there are no contraindications to heparinization, a median sternotomy approach to a central tear of a main pulmonary artery, using cardiopulmonary bypass, allows complete access to the posterior mediastinal structures including the trachea as well as the central pulmonary arteries.

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Extracorporeal Pulsatile Biventricular Support After Cardiac Transplantation

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A donor heart failed to adequately sustain hemodynamic function after cardiac transplantation. The cause of the donor heart dysfunction was unknown, and there were no definite risk factors identified to suggest the heart would not recover. A Symbion Acute Ventricular Assist Device System was used to support both ventricles. The heart gradually recovered and the system was explanted after 1 week of support. The patient recuperated and has been discharged from the hospital.

(Ann Thorac Surg 1989;47:614–6)

Failure of the donor heart to resume adequate function after heart transplantation has been associated with a dismal outcome. Various mechanical assist devices have been employed in this setting, but long-term survival has been rare. A recent transplant recipient with acute donor heart failure was successfully managed with biventricular pulsatile support until the donor heart recovered adequate function.

A critically ill 57-year-old, 66 kg woman with idiopathic cardiomyopathy and severe congestive heart failure was receiving inotropic therapy in the intensive care unit when a donor heart became available. Before transplantation she was treated with cyclosporine (Sandoz Ltd, Basle, Switzerland; 3 mg/kg, orally) and Imuran (Burroughs Wellcome, Research Triangle Park, NC; 4 mg/kg, orally); intraoperatively, she was given Solu-Medrol (Upjohn, Kalamazoo, MI; 500 mg, intravenously) at the end of bypass.

The donor was a 47-year-old, 57 kg, blood type O woman who sustained an intracerebral hemorrhage 24 hours before the donor operation. The lowest systolic blood pressure was approximately 60 mm Hg before the determination of brain death and dopamine was administered at 20 μg/kg/min. After brain death was declared, the donor was rehydrated to a central venous pressure of 12 mm Hg, and the dosage of dopamine was reduced to 5 μg/kg/min. An electrocardiogram and an echocardiogram were within normal limits before the donor operation. The donor had a negative cardiac history, no episodes of cardiac arrest, and no overt evidence of infection. Serum electrolytes were within normal limits with the exception of a mild hyperchloremia. The blood gases revealed a Po_2 of 120 mm Hg, a pH of 7.45, and a Pco_2 of 23 mm Hg on an FIo_2 of 40%. The liver and kidneys were also harvested and the donor operation went without complication.

The graft implantation went routinely, and the ischemic time was 2 hours and 52 minutes. The recipient was weaned slowly from bypass and the heart displayed evidence of severe biventricular failure with blood pressures of 70 to 80/60 mm Hg during administration of 4 μg/kg/min of isoproterenol and 4 μg/kg/min of epinephrine. Cardiopulmonary bypass was resumed and the Symbion Acute Ventricular Assist Device (AVAD) System (Symbion Corp, Salt Lake City, UT) was inserted to support both ventricles.

Insertion and management of the Symbion AVAD System was relatively straightforward. Right angle inflow cannulas (51F) were inserted into the right and left atria through plegeted pursestring sutures (Fig 1). The left assist device was positioned to the right, and the right assist device to the left. Blood returned to the body via a graft sewn to the donor pulmonary artery for the right assist device, and a graft sewn to the recipient aorta for the left assist device. The sternum was closed at the end of the procedure. The patient was then weaned from bypass, and initial pressure tracings revealed minimal contribution from the donor heart (Fig 2). The total bypass time was three hours. The anticoagulation regimen was dipyridamole (100 mg every 8 h per nasogastric tube) and heparin (titrated to keep the partial thromboplastin time about twice normal), which was started once the chest tube output had become minimal. Weaning from the device was facilitated by gradually decreasing the vacuum applied during device diastole. This reduced the stroke volume, thereby reducing the output from the device.

A cause for the donor heart dysfunction was never determined. The cytotoxic cross-match was negative. The initial creatine phosphokinase level after bypass was 2,021 with an MB fraction of 309, suggestive of a major myocardial injury. The electrocardiogram postoperatively had very low voltage with ST-T wave changes, but this gradually resolved and there were no localized areas of infarction.

The patient had a complicated postoperative course.

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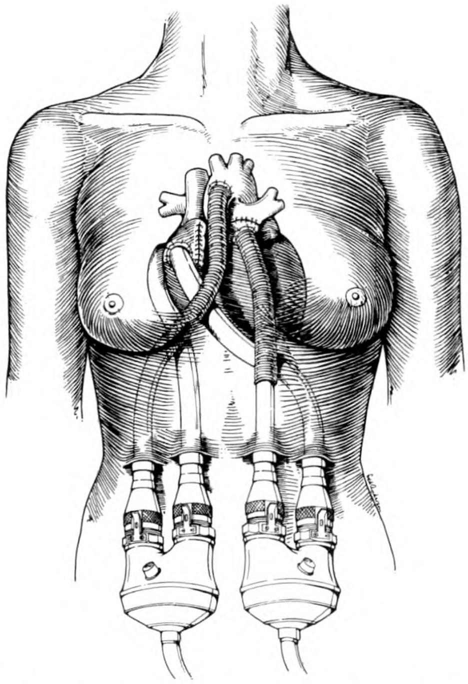

Fig 1. Positioning of Symbion Acute Ventricular Assist Device System.

Urine output was initially poor and acute nonoliguric renal failure was diagnosed. Fortunately, the patient responded to aggressive diuretic therapy and dialysis was avoided. Infectious complications consisted of *Staphylococcus aureus* at an intravenous catheter site, which was treated with vancomycin, and an extensive *Candida* infection in the sputum, which was treated with amphotericin. Over the next week, the donor heart recovered (Fig 3). The patient tolerated short periods when the AVADs were stopped, and the left ventricular ejection fraction with AVAD support was 63% by multiple gated acquisition (MUGA) scan. The devices were removed on the seventh postoperative day. The Dacron cuffs from the pulmonary and aortic grafts were excised to eliminate any foreign bodies in the mediastinum. A MUGA scan 2 weeks after AVAD removal revealed an ejection fraction of 46% with moderate apical hypokinesis and slight hypokinesis in all other segments. Other complications included *Legionella* pneumonia, rejection, and deafness, which was attributed to a combination of diuretic and antibiotic therapy. The patient recovered and was discharged but the auditory deficit did not improve.

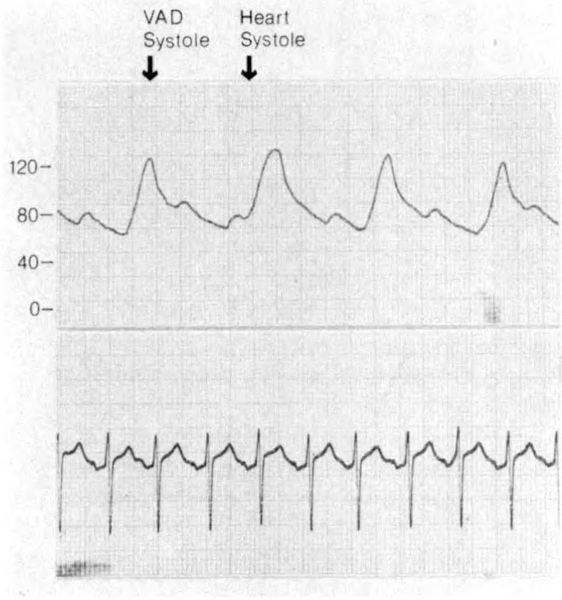

Fig 2. Arterial pressure and electrocardiogram tracing immediately after operation.

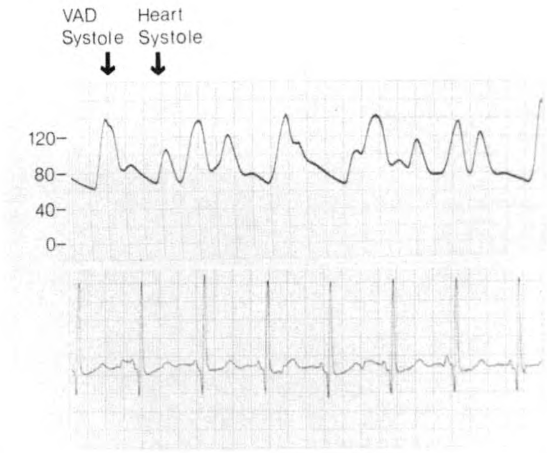

Fig 3. Altered pressure and electrocardiogram tracing seven days postoperatively.

Comment

Extracorporeal pulsatile ventricular assist devices have been successfully used as bridging devices in cardiac transplantation [1, 2] and for temporary assist in patients who fail to be weaned from bypass [3, 4]. Fortunately, mechanical assist devices are rarely required for patients after heart transplantation.

The results of mechanical assist devices after transplantation have been discouraging. Extracorporeal membrane oxygenation support after transplantation has yielded 1 survivor in 4 reported cases [5, 6]. Right ventricular nonpulsatile assist after transplantation has also had disappointing long-term results [7, 8], as has the use of pulsatile assist devices [6]. These devices were used to support patients with right ventricular failure secondary to pulmonary hypertension, implantation of an inappropriately small heart, and acute donor heart failure. One long-term survivor who suffered a cyclosporine-in-oil embolus required mechanical assist with extracorporeal membrane oxygenation after transplantation until cardiopulmonary function recovered [6].

Every effort must be taken to ensure that a donor heart will be appropriate for a particular recipient, but the knowledge of donor physiology remains incomplete and a rare donor heart will fail to adequately assume hemodynamic support after transplantation. As the effects of the critical organ shortage bear heavily on programs, one may be tempted to take a questionable donor that may have been rejected in the past.

This case represents the first incidence that we know of in which an extracorporeal biventricular pulsatile assist device has been used successfully to salvage a transplant patient with donor heart failure. The fact that the heart was able to recover, adequately support the patient, and attain near-normal functioning is encouraging. It is difficult to know which hearts have reversible versus irreversible damage in the acute setting. At the present time, a trial of biventricular support to allow sufficient time for myocardial recovery represents the only way to determine if a heart is salvagable. Univentricular support may be adequate in some patients with stunned myocardium, but it can be difficult to determine which patients will continue to be adequately supported for the few days required for recovery to occur. Biventricular support unloads both ventricles and assures the patient of an adequate output during the recovery period. Certainly further research into myocardial preservation and donor physiology is warranted. There may be a time in the future when one may harvest what is currently an unacceptable donor heart and electively utilize an assist device to allow for organ recovery. This patient's course serves as a reminder of the current limits of the understanding of donor physiology, but may lead to an era of greater utilization of scarce donor resources.

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Survival of a Recipient of Renal Transplantation After Pulmonary Phycomycosis

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A 48-year-old nondiabetic man maintained on prednisone, azathioprine, and cyclosporine after cadaveric renal transplantation developed multiple unilateral phycomycotic pulmonary abscesses. Despite treatment with amphotericin B the patient remained febrile. Surgical resection of these pulmonary abscesses was performed and the patient remains free of disease 1 year after operation. To our knowledge, this patient represents the first reported case of pulmonary phycomycosis in a recipient of renal transplantation without diabetes mellitus.

(Ann Thorac Surg 1989;47:617–9)

Phycomycosis is a rare but highly lethal disease in immunocompromised patients. In the English-language medical literature there are, to our knowledge, only two reports of recipients of renal transplantation who survived after pulmonary phycomycosis [1, 2]. Both of these patients had diabetes mellitus. We report a case of survival after pulmonary phycomycosis in a recipient of renal transplantation without diabetes mellitus.

A 48-year-old man undergoing hemodialysis because of end-stage renal disease secondary to primary systemic hypertension underwent cadaveric renal transplantation in May 1987. Maintenance immunosuppression consisted of 25 mg of prednisone, 125 mg of azathioprine, and 350 mg of cyclosporine daily. One month after transplantation he was readmitted to the hospital after several days of fever, malaise, and nausea. Physical examination revealed an afebrile well-appearing man. White blood cell count on admission was 9.7×10^9/L with 80% filamented neutrophils, 16% nonfilamented neutrophils, 1% lymphocytes, 2% monocytes, and 1% eosinophils. The blood creatinine level was 221 μmol/L and the blood urea nitrogen level was 13.57 mmol/L. The blood glucose level was 6.44 mmol/L and the bicarbonate level was 16 mmol/L.

Chest roentgenogram on admission showed two new cavity lesions in the right lung field (Fig 1). A 4-cm lesion was present in the right anterior mediastinum and a 1.5-cm lesion was present inferior and lateral to the right hilum. Computed tomography of the chest showed these lesions to be of low density and most likely inflammatory in origin. Computed tomography–guided needle aspiration of the larger lesion returned 20 mL of cloudy brown fluid which, under microscopic examination, revealed nonseptate branching hyphae compatible with *Rhizopus*. Treatment with intravenous amphotericin B was begun, and azathioprine administration was discontinued. Despite treatment with amphotericin B the patient became febrile to 39°C orally. Pulmonary function test showed forced expiratory volume at 1 second to be 2.7 L (78% of predicted) and maximum voluntary ventilation to be 125.04 L/min (105% of predicted). Nine days after admission the patient underwent a right upper lobectomy and wedge resection of the right middle and lower lobes through a right posterolateral thoracotomy. The 4-cm lesion was found to be in the anterior segment of the right upper lobe and was adherent to the superior vena cava, anterior to the right phrenic nerve. The smaller lesion was found to straddle the fissure between the right middle and lower lobes. Microscopic examination of the resected pulmonary tissue revealed multiple fungal abscesses with hyphae consistent with phycomycosis (Fig 2).

The patient's postoperative course was complicated by an episode of renal allograft rejection treated with three daily intravenous boluses (250 mg each) of methylprednisolone sodium succinate. Amphotericin B adminstration was continued postoperatively up to a total of 3 g. The patient was discharged approximately 2 months after admission. At that time the creatinine level was 309.4 μmol/L, the blood urea nitrogen level was 29.63 mmol/L, and the blood glucose level was 5.28 mmol/L. Since discharge the patient has been seen periodically as an outpatient, and at 1 year his chest roentgenogram demonstrates no evidence of recurrent infection.

Comment

Recipients of organ transplantation are prone to opportunistic infection by a wide range of pathogens. Phycomycosis is a rare but highly lethal fungal infection that has been reported in recipients of renal [1], hepatic [3], and cardiac [4] transplantation. About two dozen cases of phycomycosis have been reported in recipients of renal transplantation. Rhinocerebral disease is the most common form of phycomycosis (70%), followed by cutaneous disease (15%), pulmonary disease (10%), and hepatic disease (5%). The majority (more than 90%) of these patients have diabetes mellitus as a consequence of maintenance corticosteriod immunosuppression [1].

Pulmonary phycomycosis is thought to follow inhala-

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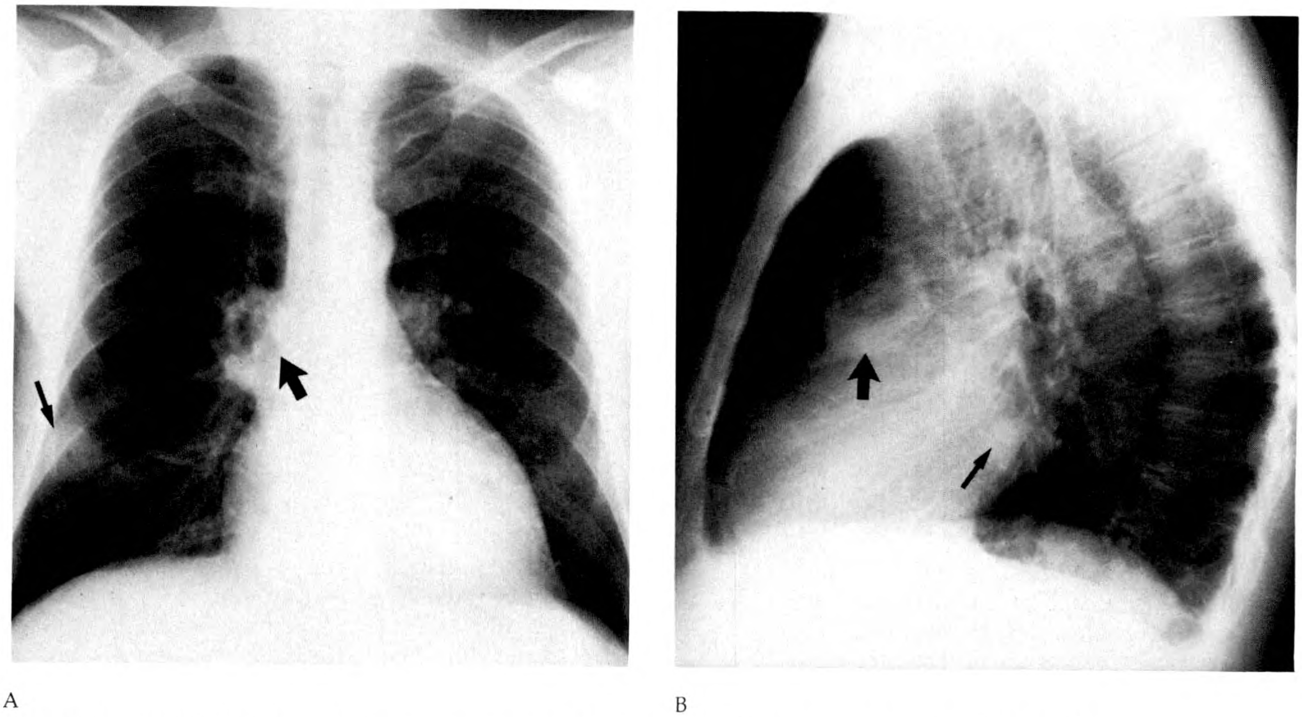

Fig 1. Posteroanterior (A) and lateral (B) chest roentgenograms showing two mass lesions (arrows) *in the right lung field.*

tion of the ubiquitous fungal spores found commonly in soil and decaying organic matter. It is characterized pathologically by vascular thrombosis and tissue infarction, and roentgenographically by cavity formation or patchy infiltration [5]. The two previous recipients of renal transplantation who survived after pulmonary phycomycosis were both diabetic. One was treated with amphotericin B only because of poor pulmonary function [1] and the other was treated with amphotericin B and surgical resection [2]. The efficacy of treating these patients with amphotericin B alone is unclear because of the questionable ability of amphotericin B to penetrate infarcted tissue and abscess cavities.

Fig 2. Nonseptate branching hyphae in lung abscess. (Methenamine silver stain; ×350 before 28% reduction.)

The relationship between diabetes mellitus and phycomycosis is complex. Diabetic patients have abnormal neutrophil chemotaxis, which probably accounts for their susceptibility to infection [6]. In cortisone-induced diabetic mice, defective alveolar macrophage inhibition of spore germination has been described [7]. Altered saturation of transferrin necessary for the antiinflammatory effect of leukocytes is associated with ketoacidosis. Use of ketones by *Mucor* for growth and proliferation has also been demonstrated [8]. Interestingly, our patient did not exhibit any fasting hyperglycemia during his entire hospitalization. In the literature there has been one previous report of phycomycosis in a nondiabetic recipient of renal transplantation who died of rhinocerebral disease [9].

In conclusion, pulmonary phycomycosis can occur in nondiabetic recipients of renal transplantation. Early diagnosis, reduction of immunosuppressive therapy, and expeditious surgical resection combined with antifungal therapy can result in the survival of immunosuppressed patients with this rare pulmonary infection.

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REVIEW OF RECENT BOOKS

Heart Valve Replacement and Future Trends in Cardiac Surgery

Edited by Gregorio Rabago and Denton A. Cooley
Mount Kisco, NY: Futura, 1987
515 pp, illustrated, $65.00

Reviewed by John G. Jacobson, MD

The editors of this volume have coordinated the views of 86 authors from around the world into seven sections dealing with aspects of heart valve replacement. The opening section establishes the favored definitions and methods of reporting, which are then used in the remainder of the volume so that the reader may become experienced in their use.

The second section is occupied by surgical techniques of valve replacement. The solutions to the complex and rare problems are dealt with in both a practical and a novel manner. The third section considers long-term experience with prosthetic heart valves. Unfortunately, it has too many series with only short-term follow-up. Despite this shortcoming, the section still manages to demonstrate effective ways of evaluating and comparing data. The hazards of anticoagulation therapy in treating thromboembolism are discussed in the fourth section. Also highlighted in this section are the differences between biological and mechanical valves. The clinical evaluation of cardiac prostheses is amplified in the chapters of section 5 through critique of the advanced technology being brought to focus on this area. The sixth section gives excellent material on the high-risk undertaking of cardiac reoperation for prosthetic valves, and the final section shares developing methods for dealing with lethal cardiac disease by describing skeletal muscle cardiomyoplasty, cardiac replacement in infants, and heart-lung replacement.

Whether read by chapter, by section, or in totality, this book provides authoritative information from eminent physicians worldwide. Although in many areas no consensus is developed, the book is enormously successful in providing an international—and therefore broader and fuller—perspective on heart valve replacement.

Deer Park, California

Internal Banding for Palliation of Truncus Arteriosus in the Neonate

J. Nilas Young, MD, M. Cristina Piancastelli, MD, James E. Harrell, Jr, MD, Christian Hardy, MD, Edward N. Ahearn, and Roger R. Ecker, MD

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A method for surgically limiting pulmonary blood flow in the critically ill neonate with truncus arteriosus is described. Two recent cases utilizing this technique are presented. Comparisons are made between this and other palliative surgical procedures used in truncus arteriosus.

(Ann Thorac Surg 1989;47:620–2)

Truncus arteriosus is often associated with severe congestive heart failure in the neonate, occasionally to the point of severe hemodynamic decompensation. These cases pose serious therapeutic dilemmas. Primary repair in the neonate has been generally associated with excessive mortality [1–3]. Pulmonary artery banding offers theoretical benefits, but overall results have been poor, with high early mortality and late survivors sustaining substantial pulmonary artery distortion, which complicates definitive repair [4–8]. This report describes 2 patients treated with a type of "internal banding" procedure, utilizing a perforated polytetrafluorethylene (PTFE; Gore-Tex, W.L. Gore & Assoc, Inc, Flagstaff, AZ) patch over the pulmonary orifice in 1 patient with type I truncus arteriosus and in a second patient with type II truncus arteriosus [9].

Material and Methods

Via a median sternotomy the patient is placed on cardiopulmonary bypass using a single arterial cannula inserted at the level of the innominate artery and a single right atrial cannula for venous drainage. Hypothermia (22° to 25°C, nasopharyngeal) with a brief period of circulatory arrest to assess anatomy is utilized. A rounded PTFE patch is fashioned and a 3-mm central hole created using an aortic punch commonly used during coronary artery bypass procedures (Hancock aortic punch, Johnson & Johnson, Anaheim, CA). The aortic cross-clamp is applied, the truncus is opened anteriorly, and the truncal valve and pulmonary orifices are evaluated. The PTFE patch with its central perforation is sewn into place over the pulmonary orifice(s) using running 6-0 Prolene (Ethicon, Inc) suture (Fig 1). The truncus is closed and the patient is weaned from bypass.

Patient 1

A 1-week-old, 3,020-g boy was seen with tachypnea and cyanosis. A grade 2/6 systolic cardiac murmur was present, and a roentgenogram revealed marked cardiomegaly and pulmonary congestion. The echocardiogram suggested type I truncus arteriosus and type B aortic interruption [10]. These were documented by cardiac catheterization. There was no truncal valvular insufficiency. During the evening of admission the child demonstrated progressive metabolic acidosis and clinical deterioration despite mechanical ventilatory support and large doses of inotropic agents. On the second day of life intermittent episodes of bradycardia occurred, one of which resulted in cardiac arrest requiring prolonged external cardiac massage. The patient was resuscitated, but became anuric and continued to have a low cardiac output. He was taken to the operating room later that day, and an internal banding procedure was performed. In addition, the patient had an 8-mm PTFE tubular graft inserted to establish aortic continuity. Postoperatively the patient's hemodynamic status rapidly stabilized, with roentgenographic evidence of clearing of congestive heart failure. Persistent renal failure was treated successfully with peritoneal dialysis, with ultimate return of normal renal function. The patient had transient hemolysis of unknown etiology, which cleared over several days. His chest roentgenogram revealed clearing of heart failure but demonstrated changes consistent with bronchopulmonary dysplasia. The patient required prolonged mechanical ventilation with tracheostomy and gastric fundoplication for gastroesophageal reflux. He was subsequently discharged, and has remained in a good nutritional state at home, growing well and awaiting definitive repair. Congestive heart failure is controlled with digoxin, furosemide, and captopril. Arterial oxygen saturation is 80%.

Patient 2

A 2,780-g girl of 36 weeks gestation developed respiratory distress within minutes of birth and required mechanical ventilation. Initially, a grade 4/6 to-and-fro murmur was audible, and echocardiographic findings demonstrated truncus arteriosus. Cardiac catheterization revealed type II truncus arteriosus with mild to moderate (2/4) truncal valve insufficiency. Despite vigorous medical management the patient continued to deteriorate, with progressive heart failure. On the 11th day of life the patient was taken to the operating room, where an internal banding procedure was performed. Postoperatively there was

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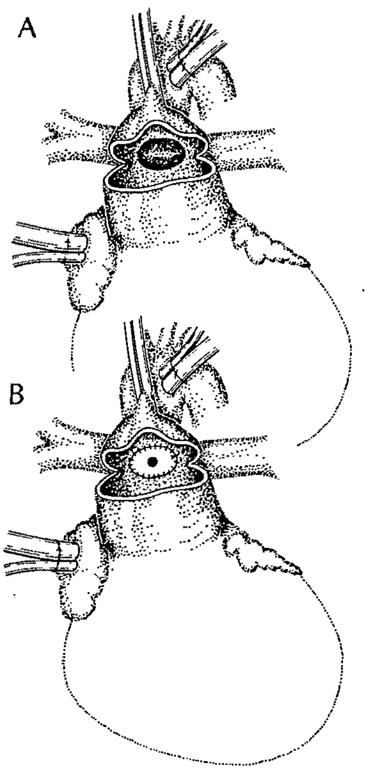

Fig 1. A. Type II truncus arteriosus. B. A perforated patch (central opening diameter, 3 mm) has been inserted to limit pulmonary blood flow.

rapid clearing of pulmonary congestion and good hemodynamics. She continued to do well from a cardiac standpoint, although she required prolonged mechanical ventilation because of tracheobronchial compression from the enlarged truncal vessel. For this latter condition she ultimately required operative truncopexy and tracheostomy. She was discharged home at 4 months doing extremely well, with an arterial oxygen saturation of 75%. She continued to gain weight and thrive at home. At 11 months of age, while awaiting definitive repair, she had an apparent episode of postprandial aspiration, followed by cardiac arrest and death.

Comment

Patients in florid heart failure secondary to truncus arteriosus in the first week of life pose a serious therapeutic challenge. To date no routinely effective palliative surgical procedure has been described, and the advisability of attempted complete repair in this setting remains unclear. Standard pulmonary artery banding is difficult because of the abbreviated length of the main pulmonary artery, if it exists at all, and usually results in distortion of the pulmonary artery bifurcation or main branches.

Other innovative procedures involving the creation of pulmonic ostial stenosis have been performed to limit pulmonary flow. Mistrot and colleagues [11] used a method for creating pulmonary ostial stenosis by suturing the pulmonary orifice over a 3-mm dilator. Litwin and Friedberg [12] used a method for creating pulmonary ostial stenosis by placing sutures on the exterior aspect of the pulmonary trunk in a patient with type I truncus arteriosus. Doty and co-workers [13] and Behrendt and Rocchini [14] have described techniques using perforated patches over the pulmonary artery bifurcation in palliative procedures for aortic atresia–hypoplastic left heart syndrome. Jonas and colleagues [15] have used centrally perforated PTFE patches over the pulmonary bifurcation in patients with hypoplastic left heart palliation. We have not used these approaches in patients with hypoplastic left heart, preferring to utilize the technique described by Norwood and co-workers [16], but we would consider their use if circumstances appeared favorable.

Both of our patients required prolonged mechanical ventilatory support but appeared to benefit from the internal banding procedure in that congestive heart failure was controlled. Despite the fact that our first patient developed postoperative transient hemolysis, previous reports [4–8] do not suggest hemolysis as a major complication of perforated patches. The effectiveness of a perforated patch to regulate pulmonary flow is unknown. Acute occlusion of the central opening is a possibility at any time and would be a catastrophic event. In the subset of patients with severe truncal valve insufficiency it is unlikely that the procedure would provide substantial palliation.

Our experiences in the 2 patients reported here suggest that the technique of internal banding might be applicable in the surgical management of selected neonates or infants with truncus arteriosus (as well as other defects) requiring surgical limitation of pulmonary flow. As the bifurcation or branch pulmonary arteries are not distorted, complex pulmonary artery reconstruction is unnecessary at the time of definitive repair. The central hole punched in the patch allows accurate calibration of the pulmonary orifice. The technique does, of course, require the use of cardiopulmonary bypass, but this was well tolerated in both patients.

Our patients did extremely well hemodynamically, with rapid resolution of congestive heart failure and adequate postoperative systemic oxygenation. Although complete repair is preferable, palliative approaches to the infant in extremis secondary to defects such as truncus arteriosus warrant continued consideration and investigation.

We thank Doreen Callahan for her assistance in preparation of this manuscript.

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INVITED COMMENTARY

This paper reports the technique to palliate neonates with truncus arteriosus using a perforated patch sewn into the pulmonary arterial ostium. This technique was used in 2 patients and both survived the operative period, although they required prolonged mechanical ventilation and hospitalization. One of the reported patients had an associated interrupted aortic arch. Perhaps the subset of patients with truncus arteriosus and interrupted arch would represent the group of patients most likely to benefit from this procedure. In other patients with truncus arteriosus, it would appear that definitive reparative operation at the time of diagnosis would be a preferred course to follow. The reported palliative operation requires the use of cardiopulmonary bypass and circulatory arrest, so that the patient is subjected to essentially the same risks that he or she would be subjected to had a definitive repair been carried out. On the other hand, the patient that has undergone successful reparative operation is much less likely to have the major pulmonary complications that were seen in these patients and would be more hemodynamically stable and likely to tolerate complications better.

In recent years, a number of centers have reported acceptable results with early reparative operation in truncus arteriosus using aortic valved homografts or Dacron grafts containing heterograft valves. We should not lose sight of the fact that when we subject a patient to the risks of cardiopulmonary bypass and circulatory arrest, we should perform an operation that will leave the patient as close to repaired as possible.

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Localized Pericardial Flap to Prevent Tension on Left Internal Mammary Artery Grafts

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Tension on a left internal mammary artery graft may be caused by the medial edge of the left lung. A localized pericardial flap may be used to prevent this problem while still allowing adequate pulmonary expansion.

(Ann Thorac Surg 1989;47:623–4)

The left internal mammary artery (LIMA) is commonly used for revascularization of the left anterior descending coronary artery [1]. In a subgroup of patients, expansion of the left lung during inspiration may cause tension on the graft (Fig 1). This situation may occur in the patient whose lungs are chronically overinflated secondary to chronic obstructive pulmonary disease, or where the LIMA is of minimal useful length due to its small size.

A technique is described that uses a localized pericardial flap mobilized from the free edge of the left pericardium to restrict expansion of the left upper lobe and thus protect the LIMA from excessive tension.

Technique

Tension on the LIMA graft (Fig 1), if not predicted on first observation of the lungs at the time of opening the chest, is easily noted when the lungs are first inflated immediately before coming off bypass. The tension on the pedicle may even be enough to threaten the integrity of the anastomosis between the LIMA and the left anterior descending coronary artery.

Once such tension is noted, the lungs are allowed to collapse, and with the patient on cardiopulmonary bypass, a 6- to 7-cm incision is made in the left pericardium to produce a flap 1 cm wide in the anterior edge of the left pericardium (Fig 2). The incision is made with electrocautery, and is 2 to 3 cm anterior to the left phrenic nerve, which is visible on the left side of the pericardium. Alternatively, the incision can be made with scissors or a bipolar cautery if proximity of the cautery to the phrenic nerve is a concern to the individual surgeon. The small pericardial flap so created is then attached to the inner side of the second costal cartilage with a 1-0 silk suture on a cutting needle (Fig 2, inset). The tension needed to create a protective channel for the LIMA pedicle requires a little experimentation, but the correct tension will hold back the upper part of the left lung without unduly restricting expansion.

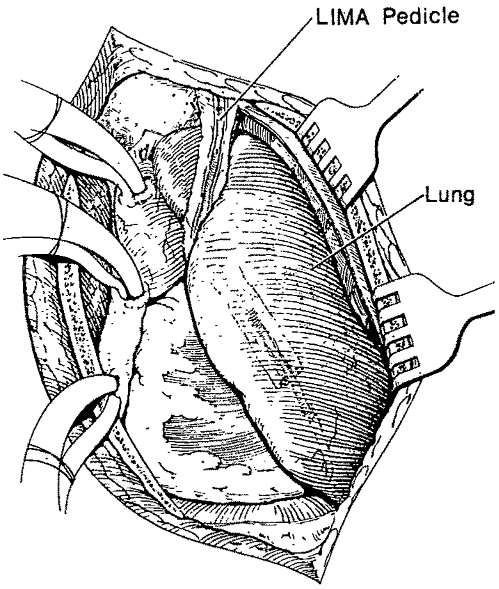

Fig 1. The pedicle of the left internal mammary artery (LIMA) may be placed under tension by the medial edge of the left lung during inspiration.

After placement of the restraining suture, the lungs may be expanded and the patient weaned from cardiopulmonary bypass without danger of tension on the LIMA graft. The pericardium or mediastinal fat may be closed for most of its length at the surgeon's discretion (Fig 3).

Comment

This technique can be used routinely in patients with hyperexpansion of the left lung to prevent any tension on the LIMA graft while retaining the benefits of left lung expansion and allowing closure of the pericardium [2].

An alternative method described by Todd and associates [3] suggests the suturing of the whole length of the left anterior pericardial edge to the back of the sternum to restrict expansion of the left lung and achieve the same result. This method is effective in preventing tension on the LIMA graft from the left lung, but has several drawbacks. First, restricting the expansion of the left lung in this way may have pulmonary consequences postoperatively, especially in the patient with compromised pulmonary function. Second, the left lung is prevented from herniating across to the midline and thus interposing between the back of the sternum and the anterior surface of the right ventricle. This may allow adherence of the

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anterior right ventricle to the back of the sternum, an undesirable anatomical arrangement if reoperation becomes necessary. Third, attaching the pericardial edge to the sternum prohibits closure of the pericardium where desired [2].

One reviewer of this article suggested creating a hole in the pericardium so that the LIMA travels almost directly from the subclavian artery to the left side of the heart, beneath the apex of the lung, thus avoiding impingement of the lung on the LIMA. We have had no direct experience with this technique.

The present technique has been used for over 2 years and in approximately 50 patients without specific complications. In most of these patients, the pericardium was closed, but this is by no means essential. This technique has been shown to be a helpful adjunct in cases in which tension on the LIMA from the left upper lobe threatens the integrity of the LIMA–left anterior descending coronary artery anastomosis. Presumably the technique could be modified for use on the right side, but in the 1 patient in whom it was attempted, tension on the pericardial flap appeared to distort the superior vena cava, and the effort was abandoned.

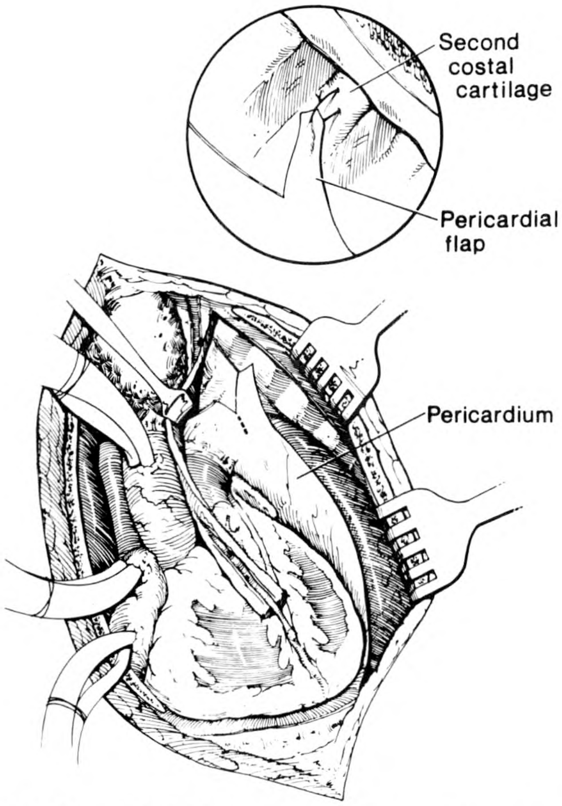

Fig 2. Collapse of the left lung allows visualization of the free edge of the pericardium and creation of a flap approx 1 cm wide and 6 to 7 cm long (shown by dotted line*). The pericardial flap is attached to the posterior surface of the second costal cartilage to create a tunnel for the graft (inset).*

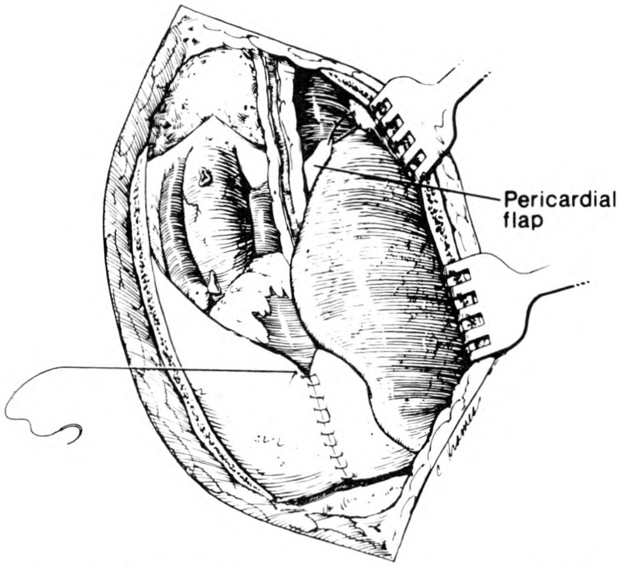

Fig 3. The pericardial flap allows almost unrestricted expansion of the left lung but prevents tension on the left internal mammary artery pedicle. Closure of the pericardium is still possible if desired.

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A Technique for Aortic Root Replacement by an Aortic Allograft

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Allograft replacement of the aortic root is a logical extension of subcoronary allograft aortic valve replacement. The aortic root can be replaced by a cryopreserved allograft aortic root using an inclusion technique employing a continuous Prolene suture for each of the suture lines. This technique provides an expeditious operation and hemostatic suture lines.

(Ann Thorac Surg 1989;47:625–7)

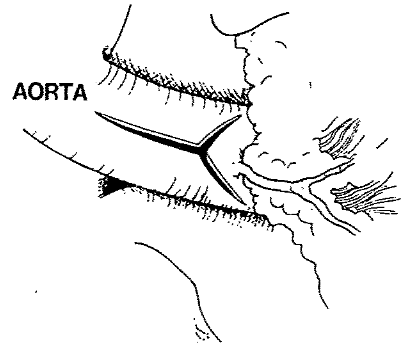

Fig 1. Aortic incision. Extension of the incision to the left of the right coronary ostium greatly facilitates exposure.

Aortic root replacement by an allograft aortic root [1] is a natural extension of replacement of the aortic valve by an allograft aortic valve [2, 3] and aortic root replacement as originally described by Bentall and de Bono [4]. Although the consequences of the likely calcification of the allograft aortic wall are unknown, the good long-term results of subcoronary implantation of the cryopreserved allograft aortic valve [5] suggest that this course is appropriate for situations in which aortic root replacement is considered. Primary aneurysmal aortic wall disease, left ventricular outflow tract obstruction, and aortic root destruction due to infective endocarditis constitute indications for aortic root replacement.

Material and Methods

Methods of procurement, sterilization, and cryopreservation of allograft aortic valves used at The Prince Charles Hospital have previously been described [6]. The operation is performed through a median sternotomy, using hypothermic cardiopulmonary bypass to 25°C with ascending aortic, single right atrial, or dual caval cannulation and left ventricular venting through the right superior pulmonary vein or apex of the left ventricle. After clamping of the ascending aorta, a vertical aortotomy is made curving down toward the noncoronary sinus. Once the final decision to perform a root replacement is made, the incision is extended toward the left side of the right coronary ostium (Fig 1). Cold crystalloid cardioplegic solution is administered by direct coronary cannulation and is supplemented by topical ice slush cooling.

The valve is excised and the annulus measured. As aortic and annular dilation are invariably present, an allograft aorta with an internal diameter of 24 mm or greater is selected. After the allograft is thawed, its muscle and anterior mitral leaflet at the base are trimmed, leaving the muscle somewhat thicker (3 to 4 mm) than for a subcoronary allograft aortic valve implantation. Stay sutures are placed on the edges of the incised aorta. The proximal annular suture line is commenced after the allograft is rotated 120 degrees, the right coronary artery ostium of the allograft being opposite to that of the host left coronary artery. This continuous suturing is performed with a double-armed 4-0 Prolene suture (no. 8521, Ethicon) on a large taper SH needle, commencing on the left lateral side at the junction of the allograft muscle and mitral valve remnant. Rotation of the allograft allows more accurate visualization of the muscle and its endocardial surface than if the allograft is not rotated and the muscle is left anteriorly (Fig 2). When the posterior segment of this suture line is complete, the other limb of the suture is continued anteriorly. All suturing is per-

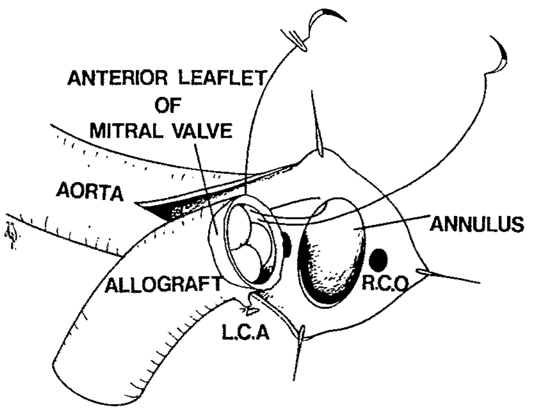

Fig 2. Lower suture line performed. (L.C.A. = *left coronary artery;* R.C.O. = *right coronary ostium.)*

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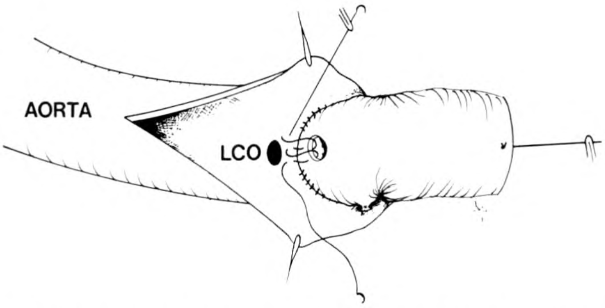

Fig 3. Left coronary anastomosis performed. (L.C.O. = *left coronary ostium.)*

formed with a continuous forehand technique. If the sutures are placed close together (approximately 2 mm apart), hemostasis can be anticipated.

The left coronary artery of the allograft is ligated or, alternatively, the ostium is closed by 5-0 Prolene suture. The right coronary artery of the allograft is excised to create a hole for anastomosis to the left coronary ostium. The allograft is folded forward and the left coronary anastomosis is performed with either a continuous 4-0 Prolene suture (no. 8557) on a small tapered RB-1 needle or a 5-0 Prolene suture (no. 8721) on a small taper-cut CC-1 needle (Fig 3). An appropriately positioned new hole is made in the noncoronary sinus of the allograft for the right coronary anastomosis.

After completion of this anastomosis, lateral extensions are made to the upper end of the aortotomy to aid exposure of the distal anastomosis. Because the allograft has been rotated, it curves to the right. Consequently, the aorta has to be appropriately beveled, and the suture line must be performed with tension on the left wall of the allograft to avoid possible inward kinking on this left-hand side. This anastomosis is performed with continuous 4-0 Prolene suture on either the small or large needle (Fig 4). All suture lines are performed with a continuous forehand technique. The usual air removal procedures are performed, and the aortic cross-clamp is released. The host aortic wall is not wrapped around the allograft.

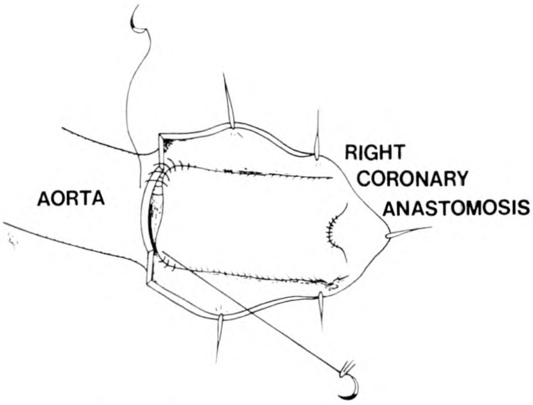

Fig 4. Right coronary anastomosis completed, small lateral extensions made to upper end of the aortotomy followed by the distal anastomosis.

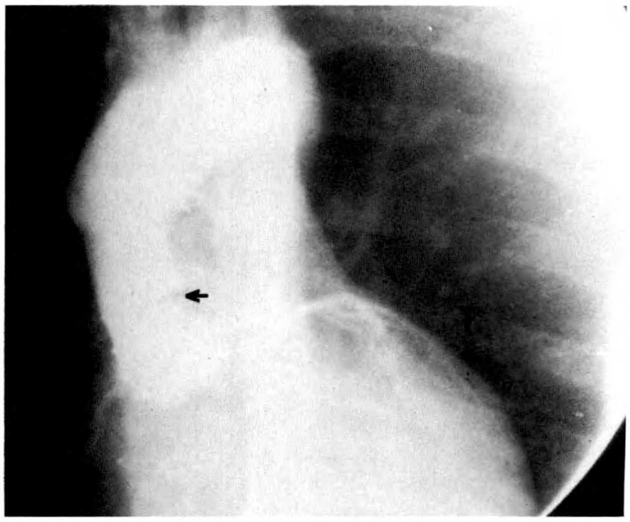

Fig 5. Ascending aortogram after aortic root replacement showing a kink in the allograft wall (arrow), *which was not hemodynamically significant.*

Comment

A number of techniques have been described for aortic root replacement with an allograft aortic valve. Most descriptions involve excision of the ascending aorta, suturing of the allograft to the aortic annulus, and reimplantation of the coronary arteries with buttons of aortic wall followed by the distal anastomosis [7–9].

At The Prince Charles Hospital from October 1985 through September 1988, 24 allograft aortic root replacement operations have been performed without early or late mortality or serious morbidity. Throughout this clinical experience an inclusion technique has been used with a variety of suturing techniques for the proximal anastomosis, including interrupted simple and interrupted mattress suturing, both methods buttressed by felt strips. These methods were found to be time-consuming and cumbersome. Hence, the continuous technique was developed, and this has been used in the last 10 patients.

As a result of the rotation, after the proximal anastomosis is completed the allograft aorta curves to the right (see Fig 2). In performing the distal anastomosis, the aorta is brought back to the midline with the tendency toward an inward kink of the allograft medial wall. This has occurred in two patients (Fig 5) and is avoided by appropriate bevelling of the graft with some tension of the medial wall.

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Notice From the American Board of Laser Surgery

The American Board of Laser Surgery announces its fourth Certifying Examination on Saturday, October 14, 1989, at Emory University School of Medicine, Atlanta, Georgia. Candidates may obtain information or application forms from Stanley Stellar, MD, President of the Board, St. Barnabas Medical Center, Livingston, NJ 07039; or Mary M. Cayton, RN, Assistant to the President, 2722 W Oklahoma Ave, Suite 202, Milwaukee, WI 53215.

An Early Approach to the Repair of Ruptured Mitral Chordae

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During the 10 years before 1958, the relief of mitral stenosis via "closed" access had provided increasingly successful results. Such was not the case for the management of mitral regurgitation. However, during the latter half of that same decade, the "door" to the interior of the heart had been "opened," which then allowed the application of techniques for the repair of mitral regurgitation under direct vision. These methods included debridement, mobilization, and direct suture of abnormal leaflets; patch closure of leaflet perforations; augmentation of leaflet area with either an extension, a gussett, or a buttress of biological or prosthetic material; and various types of annuloplasty designed to constrict the mitral annulus to reduce the valve's orificial area and thus allow more complete apposition of deformed mitral leaflets. The early success achieved by such techniques proved variable, and their long-term results were, of course, unknown. Total replacement of the mitral valve had not yet been successfully accomplished by 1958. (More complete accounts of the early development of mitral valvular surgery are available elsewhere, including in Ellis' fine monograph [1].)

Such, then, was the status of mitral surgery in 1958. In October of that year, and again in the following January, a patient was encountered at operation who proved to have ruptured chordae as the apparently principal cause of mitral regurgitation [2]. The first patient was 53 years of age and the other, 27 years. Both had had rheumatic fever during childhood; the younger patient had also had bacterial endocarditis 4 years preoperatively, and each had experienced the rather sudden onset of advanced cardiac disability some 6 months earlier. Markedly elevated left atrial V waves were noted in each patient, peaking to 85 mm Hg in the first patient and 40 mm Hg in the other.

At operation, rupture of mitral chordae involving a segment of the posterior leaflet was encountered in the first patient, and of the anterior leaflet in the second. The necessity of devising a repair for the problem of ruptured chordae was unavoidable. Obviously the segment of leaflet that was disengaged from its chordal-papillary muscular anchorage had become flail, ie, it would violently whip without restraint up into the atrium during systole. This flail portion of leaflet could therefore not appose its opposite leaflet during systole.

The question thus arose: "How might the thrashing of that flail segment of leaflet up into the atrium be corrected?" A promising technique presented itself (Fig 1).

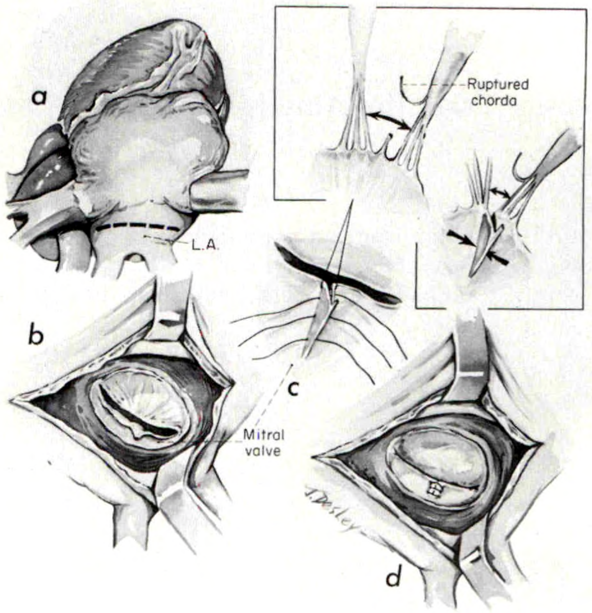

Fig 1. Plication technique of mitral valvuloplasty for regurgitation due to a ruptured chorda tendinea. (a) The surgeon's orientation as obtained via a median sternotomy or left anterolateral thoracotomy (the patient's head would be to the left). (b) A left atriotomy exposes the flail portion of the posterior leaflet. (c) The margins of the flail segment are identified and a few simple sutures are placed to approximate these margins. The subvalvular view (inset at upper right) demonstrates how approximation of the adjacent intact chordae identifies the margins of the flail segment along its free edge. (d) When the sutures are tied, the flail segment is obliterated by plicating (bunching) it upon itself. This drawing, originally commissioned by Dr F. H. Ellis (Ellis FH Jr, Frye RL, McGoon DC. Results of reconstructive operations for mitral insufficiency due to ruptured chordae tendineae. Surgery 1966;59:165–72), is used here with permission from The C.V. Mosby Company as it illustrates the technique better than the one used in the original report [2]. (L.A. = *left atrium.*)

The two steps of the technique were, first, to estimate as precisely as possible the margin at each side of the triangular-shaped flail segment, between it and the adjacent normally tethered portion of leaflet; and, second, to approximate these margins by suturing one to the other. Whether this approximation would prove more effective if accompanied by actual excision of the flail segment or by merely plicating it upon itself was, of course, unknown. Plication was chosen in these two early operations, despite the resulting slight bulkiness of the plicated portion of leaflet, because of concern that one or more sutures in such a stressed suture line might cut through the leaflet

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tissue postoperatively. If that were to happen, regurgitation would probably be lessened if leaflet substance were not resected.

In the second patient a cleft in the posterior leaflet, opposite the ruptured chordae, also was repaired by direct suturing; two sutures were also placed at the medial commissure to approximate the edges of the anterior and posterior leaflets there.

After circulation was resumed, the left atrial V waves had returned to normal in both patients, and a systolic thrill could no longer be felt behind the left atrium. The patients' postoperative courses were both uneventful, though each had a residual grade 2 murmur typical of mitral regurgitation. The first patient enjoyed marked improvement (class II) until he died of metastatic prostatic carcinoma 5 years later. The younger patient was improved at first, but then noted increasing difficulty in carrying out his farming duties. My colleagues and I reoperated 9 years after the repair, and at that time found the anterior leaflet to be pliable and only slightly thickened, even where it had been plicated. Both leaflets appeared stretched and capable of overshooting into the left atrium during systole. The valve was replaced. Again the patient was improved (class II) and could farm comfortably. He died, apparently suddenly, 3.5 years after valve replacement. No autopsy was performed. Nothing more is known about the cause of death; the death certificate succinctly attributes the cause to "myocardial infarction."

Included in the 1960 report of these two patients [2] is the statement: "it seems reasonable to believe that mitral annuloplasty in combination with mitral valvuloplasty may be advantageous in certain instances." Clearly, an annuloplasty should also have been employed in at least the second patient's repair, a step that probably would have improved his operative result.

In a review of the Mayo Clinic experience that began with these 2 patients, Orszulak and colleagues [3] found that of 131 operations for mitral regurgitation due to ruptured chordae, annuloplasty of one type or another had been included in the repair in 88%. Also, 95% of the flail segments were plicated rather than excised. Chordal rupture involved the anterior leaflet in one third of the cases. Overall early mortality was 6.1%, falling to 1% from 1965 onward. At the time of hospital dismissal, a murmur of mitral regurgitation could be heard in 58%. Late survival at 15 years was 48% (about 20% less than that of an age- and sex-matched control population). None of the many factors available for multivariate analysis proved to be significantly predictive of outcome.

Ongoing advances in concept, technique, and devices, particularly as promulgated by Carpentier and colleagues [4], have undoubtedly advanced the "state of the art" of valvular reconstruction. Although space is not available here to attempt a detailed literature analysis of the effect of technique on result (a complex challenge at best), the degree of success must surely be influenced by the experience, persistence, cleverness, and skill of the surgical team in dealing with the particular problems presented by ruptured chordae.

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Surgical Therapy in the Management of Coronary Anomalies: Emphasis on Utility of Internal Mammary Artery Grafts

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Three patients with an anomalous main coronary artery coursing between the great vessels are presented with a review of the literature. Their surgical treatment by coronary artery bypass grafting with use of the ipsilateral internal mammary artery is described with angiographic follow-up. Young patients with these anomalies, whether they are asymptomatic or have syncope, are at high risk for sudden death. Older patients with angina appear to be adequately risk stratified by thallium stress tests. For patients requiring surgical intervention, aortoplasty and coronary artery bypass grafting have both resulted in relief of symptoms, but the follow-up is limited. We suggest that coronary artery bypass grafting with an ipsilateral internal mammary artery graft to the anomalous vessel is the procedure most likely to relieve ischemia and achieve good long-term results for both symptomatic relief and survival.

(Ann Thorac Surg 1989;47:630–7)

Coronary anomalies can be associated with clinical syndromes, including sudden death. Krause [1] described a coronary arteriovenous fistula in 1865. By 1970, Ogden [2] had collected 224 cases of coronary anomalies and classified them into major, minor, and secondary types. According to Ogden, major coronary anomalies have either an abnormal communication between a coronary artery and a cardiac chamber or an abnormal origin of the coronary artery from the pulmonary artery. In a secondary anomaly, the coronary artery variation represents a circulatory response to primary intracardiac pathology. In a minor coronary anomaly, there is variation of the origin of the vessels from the aorta, but the distal circulation is normal.

Minor anomalies represent one third of all coronary anomalies [2]. Most of them are benign variants of normal anatomy. However, two minor anomalies—the left main coronary artery (LMCA) arising from the right aortic sinus and the right main coronary artery (RCA) arising from the left aortic sinus (LAS)—have been associated with both clinical symptoms and death [3].

In normal anatomy, the LMCA has its ostium in the LAS and courses between the pulmonary artery anteriorly and the left atrium posteriorly for an average distance of 10 to 20 mm before reaching the left atrioventricular groove and bifurcating into the left anterior descending and circumflex coronary arteries. The RCA originates from the right aortic sinus and courses directly into the right atrioventricular groove.

In anomalous origin of the RCA from the LAS, the RCA will course anteriorly and to the right, and will almost always run between the pulmonary artery anteriorly and the aorta posteriorly (Fig 1A). With anomalous origin of the LMCA from the right aortic sinus, the LMCA can take one of four different paths to reach the left atrioventricular groove. It can go anterior to the pulmonary artery, posterior to the aorta, or between the great vessels, or it can take a septal course through the conal septum (Fig 1B) [4]. The latter two courses and the anomalous RCA have been the minor anomalies most often associated with serious clinical symptoms. This report describes patients treated surgically for these anomalies.

Material and Methods

The files of the Thoracic Surgery Service at Brooke Army Medical Center from July 1984 through December 1986 were reviewed to locate patients with abnormal origin of a main coronary artery that coursed between the great vessels. Chart review documented presenting symptoms and signs, diagnostic procedures used, and operative findings. Follow-up for all patients was obtained by postoperative stress testing, angiography, and an interview by one of us.

Results

There were 3 patients in our series, all men, aged 38, 48, and 51 years. Two patients were seen with angina pectoris; 1 had exertional angina, and the other had angina both with exertion and at rest. The 38-year-old patient was seen with exertional syncope. Two patients had no prior cardiac history; the third had a history of paroxysmal atrial fibrillation.

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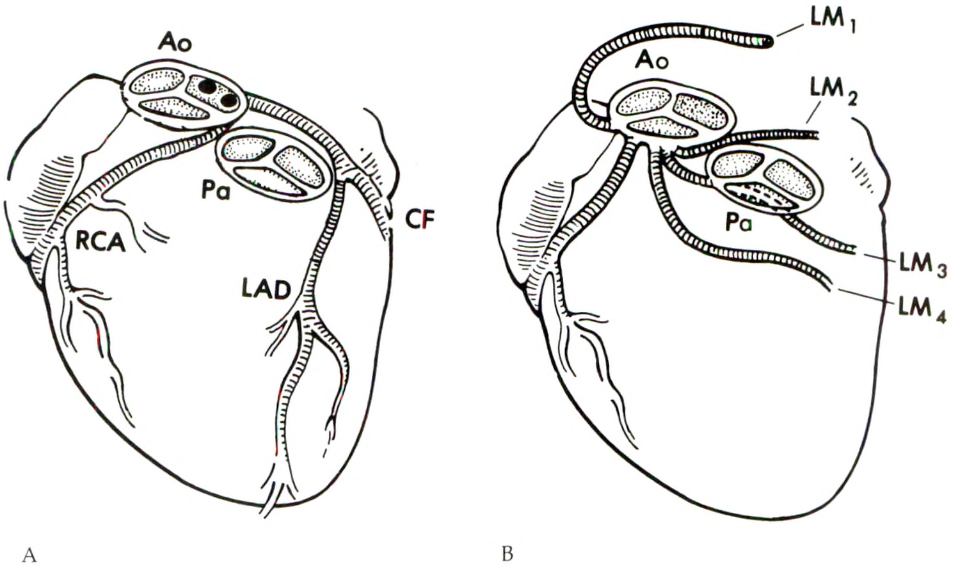

Fig 1. Anomalies of the main coronary arteries: (A) origin of right coronary artery (RCA) *from the left aortic sinus and (B) possible courses of the left main coronary artery* (LM) *arising from the right coronary sinus:* LM_1 = *left main coronary artery coursing posterior to the aorta;* LM_2 = *left main coronary artery coursing between the aorta* (Ao) *and pulmonary artery* (Pa); LM_3 = *left main coronary artery with septal course through the outflow tract of the right ventricle; and* LM_4 = *left main coronary artery coursing anterior to the pulmonary artery.* (CF = *circumflex coronary artery;* LAD = *left anterior descending coronary artery.)*

All 3 patients underwent an exercise thallium stress test and angiography preoperatively. Two patients had an anomalous LMCA arising from the right aortic sinus. One of them had associated coronary artery disease (CAD) (Fig 2); the exercise stress test indicated ischemia, and the thallium stress test showed reversible ischemia (Fig 3). The other patient had no associated CAD (Fig 4). His exercise stress test showed no ischemia at maximum exercise, but a thallium stress test demonstrated reversible ischemia. The third patient had an anomalous RCA arising from the LAS with no associated CAD (Fig 5). The results of his exercise stress test were normal, but the thallium stress test showed reversible ischemia.

Both patients with an anomalous LMCA were treated with ipsilateral internal mammary artery (IMA) grafts to the left anterior descending coronary artery and reverse saphenous vein grafts (RSVGs) to the circumflex system. In 1 of these patients in whom the origin of the anomalous vessel was dissected, the LMCA originated perpendicular to the aorta. The patient with an atherosclerotic lesion of

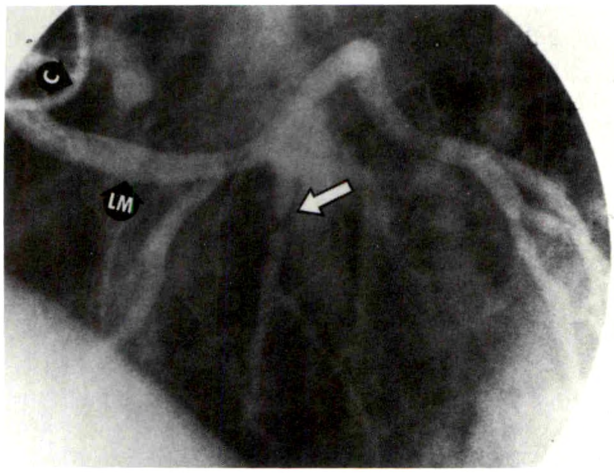

Fig 2. Left anterior oblique view of the left coronary artery system. The angiography catheter (C) *is in the right aortic sinus. The left main coronary artery* (LM) *arises from the right aortic sinus. The* arrow *demonstrates the atherosclerotic lesion in the diagonal coronary artery.*

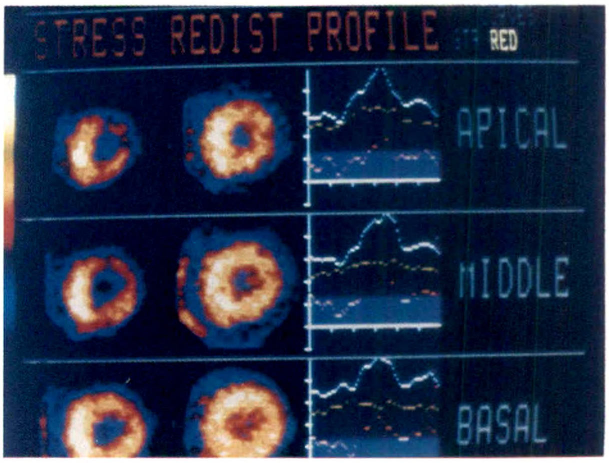

Fig 3. Thallium stress test in a patient with anomalous left main coronary artery. Circumferential quantitative analysis of the third, fourth, and fifth slices shows only the inferoseptal wall (from 180 to 270 degrees) has washout values in the normal range (above the light blue band on each graph). The entire left coronary artery system displays reversible ischemia. Stress, redistribution, and washout curves are color-coded white, yellow, and pink, respectively.

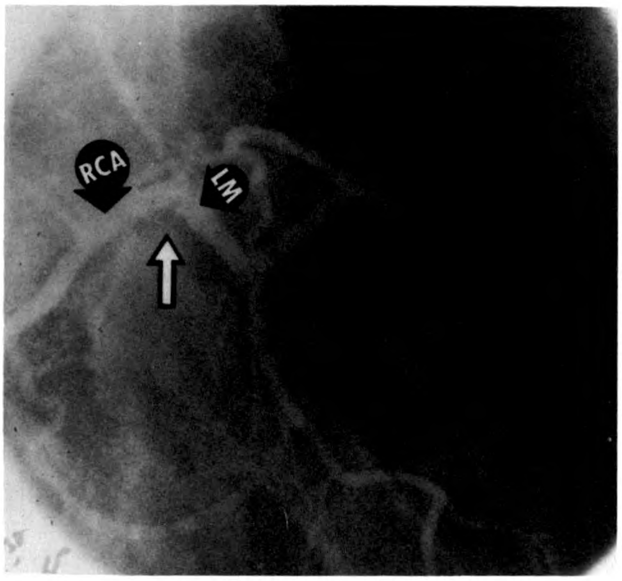

Fig 4. Right anterior oblique view demonstrating origin of the left main coronary artery (LM) *and the right coronary artery* (RCA) *from a common origin* (arrow) *in the right aortic sinus.*

a diagonal branch had this artery bypassed with an RSVG. In the patient with the anomalous RCA, the RCA originated from the LAS adjacent and anterior to the LMCA. The RCA was intimately associated with the aortic wall for 1.5 cm in its course between the aorta and the pulmonary artery, and then continued along the right atrioventricular groove. In this patient, the right IMA was used to bypass the RCA in its proximal portion with ligation of the origin of the RCA (Fig 6).

One patient required reexploration for mediastinal hemorrhage. Follow-up ranged from 9 to 14 months. At follow-up, all 3 patients were asymptomatic, had normal thallium stress tests, and had angiographically patent IMA grafts. The RSVG to a diagonal branch was occluded at follow-up.

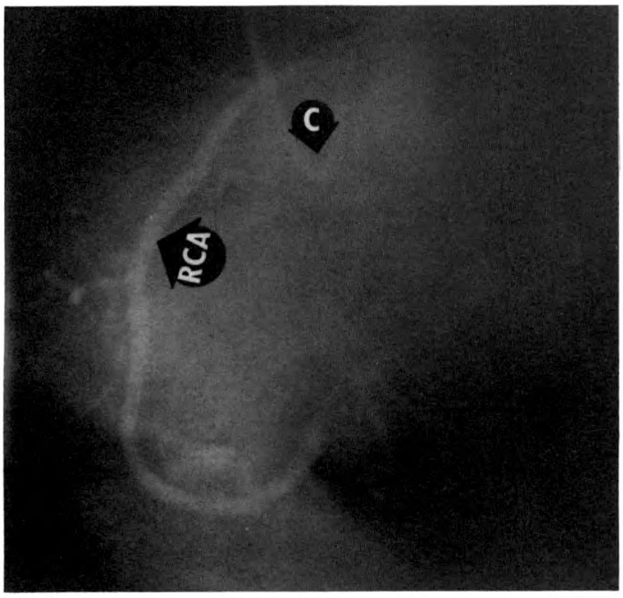

Fig 5. Left anterior oblique view demonstrating the angiography catheter (C) *in the left aortic sinus. The right coronary artery* (RCA) *is seen to arise from the left aortic sinus.*

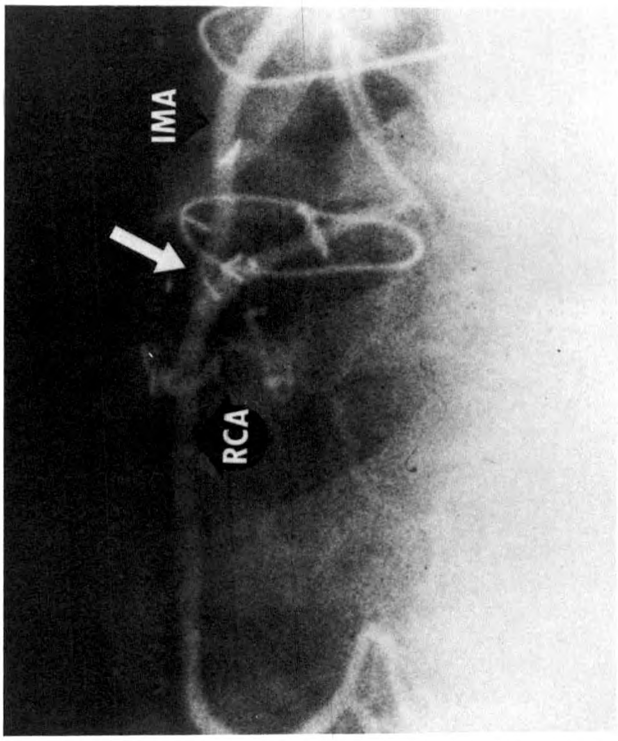

Fig 6. Left anterior oblique view of the anastomosis of the right internal mammary artery (IMA) *with the right coronary artery* (RCA). *The* arrow *marks the area of anastomosis.*

Comment

In 1962, Jokl and colleagues [5] described the lethal potential of minor coronary anomalies with the autopsy finding of an anomalous origin of the LMCA in a young athlete who died suddenly. In 1974, Cheitlin and coworkers [6] described a young man with an RCA anomaly and otherwise normal coronary arteries who had an inferior myocardial infarction (MI). They also described a 14-year-old boy who sustained an MI related to exertion and who had an anomalous LMCA treated surgically with an aortoplasty; 9-year follow-up showed no further exertional symptoms [7]. In 1983, Bloomfield and associates [8] reported the surgical treatment of an anomalous RCA; a 58-year-old man with intractable angina and otherwise normal coronary arteries obtained relief of symptoms after coronary artery bypass grafting (CABG).

A review of the literature supports our aggressive therapeutic approach in symptomatic older patients and all younger patients with these anomalies. Eighty-seven autopsy cases in which an anomalous main coronary artery passed between the great vessels have been reported. Forty-six involved an anomalous LMCA; among these, 36 of the deaths were clearly coronary in origin [9–14]. Twenty-nine of these 36 patients were less than 30 years of age. Twenty-eight of them died suddenly, 1 had

Table 1. Preoperative Noninvasive Testing for Patients With Anomalous Main Coronary Artery and Angina[a]

Reference	Year	Age (yr)	Sex	Anomalous Vessel	Symptom	Graded Exercise Stress Test	Thallium Stress Test	Associated Coronary Artery Disease
Chaitman et al [29]	1976	39	M	LMCA	Angina	Positive	Not done	Present
Thompson et al [32]	1976	37	M	RCA	Angina	Positive	Not done	Absent
		56	M	RCA	Angina	Nondiagnostic	Not done	Absent
Moodie et al [25]	1980	57	M	LMCA	Angina	Positive	Not done	Present
Keren et al [36]	1982	60	M	RCA	Angina	Positive	Not done	Present
Bloomfield et al [8]	1983	58	M	RCA	Angina	Postive	Positive	Absent
Liberthson et al [17]	1983	54	F	LMCA	Angina	Nondiagnostic	Positive	Present
Donaldson et al [21]	1983	. . .	M[b]	LMCA	Angina	Positive	Not done	Absent
		. . .	M[b]	LMCA	Angina	Positive	Not done	Absent
Grey et al [22]	1984	33	F	LMCA	Angina	Not done	Positive	Absent
Iskandrian et al [23]	1986	67	M	LMCA	Angina	Positive	Positive	Absent

[a] In 1979, Liberthson and associates [24] described 6 patients who were seen because of angina and an LMCA anomaly. Four exercise stress tests were positive, and two thallium stress tests were positive. Four of these patients had associated coronary artery disease. No other data are available. [b] Ages of the patients in this series were 15, 21, and 32 years, and could not be assigned to individual patients.

LMCA = left main coronary artery; RCA = right coronary artery.

an MI before death, and none had associated CAD [9, 13, 14]. Of the 7 patients older than 30 years, 5 had associated CAD, and 3 had a documented MI before death [6, 15]. Of the evaluated patients, half of the young patients had symptoms before death, and all patients older than 30 years had symptoms before death. In the younger patients, the symptoms were evenly distributed between syncope and angina, whereas in the older group the symptoms were predominantly angina or MI [3, 6, 9, 13–15].

Of the 41 patients with an anomalous RCA, 8 died of heart-related causes, and all 8 died suddenly [13, 16–19]. Seven of these 8 patients were younger than 30 years, and none had associated CAD or MI before death. Two young patients had prior symptoms, syncope in 1 and angina in the other [16, 19].

For both anomalies, younger patients died suddenly, without associated CAD, and half had been asymptomatic before the fatal event. Symptoms, when present, were evenly distributed between syncope and angina. Older patients had associated CAD and anginal symptoms, and half had a documented MI.

Eighty-three patients with a main coronary anomaly coursing between the great vessels have been diagnosed antemortem. Of this group, 37 had LMCA anomalies, and the patient profile was similar to those who died suddenly [4, 7, 20–28]. Young patients were seen mostly with syncope and without associated CAD. The older patients

Table 2. Preoperative Noninvasive Testing for Patients With Anomalous Main Coronary Artery and Syncope

Reference	Year	Age (yr)	Sex	Anomalous Vessel	Symptoms	Graded Exercise Stress Test	Thallium Stress Test	Associated Coronary Artery Disease
Cheitlin et al [6]	1974	14	M	LMCA	Syncope	Normal	Not done	Absent
Pedal [37]	1976	10	F	LMCA	Syncope	Normal	Not done	Absent
Murphy et al [28]	1978	12	F	LMCA	Syncope	Normal	Not done	Absent
Benge et al [33]	1980	25	M	RCA	Syncope	Normal	Nondiagnostic	Absent
Mustafa et al [26]	1981	12	M	LMCA	Syncope	Normal	Normal	Absent
Donaldson et al [21]	1983	. . .[a]	M	LMCA	Syncope	Positive (ventricular tachycardia)	Not done	Absent
Brandt et al [34]	1983	35	M	RCA	Syncope (ventricular tachycardia)	Normal	Not done	Absent
Bett et al [35]	1985	65	M	RCA	Syncope	Positive (ventricular tachycardia)	Negative	Absent
Barth and Roberts [9]	1986	14	M	LMCA	Syncope/angina	Normal	Not done	Absent

[a] Ages of the patients in this series were 15, 21, and 32 years, and could not be assigned to individual patients.

LMCA = left main coronary artery; RCA = right coronary artery.

usually had associated CAD, with angina as a predominant symptom. Although the majority of the patients diagnosed at autopsy were less than 30 years old, the majority of the patients seen clinically were more than 30 years old, a finding suggesting that patients seen at an early age frequently have sudden death as the initial presentation.

Among the 46 patients with an anomalous RCA, 19 were of unknown age. Of the remaining 27, only young patients were seen with syncope; the older ones predominantly had angina. A preponderance of young patients in the autopsy series and of older patients in the clinical series was again present [6, 8, 24, 29–36].

Stress testing to assess ischemic consequences of these anomalies has had limited success. Results of such tests have been reported for 20 patients with an anomalous main coronary artery coursing between the great vessels (13, LMCA; 7, RCA). Patients who had chest pain, with or without associated CAD on angiography, had positive exercise stress tests indicative of ischemia. In the few patients in whom these stress tests were equivocal or not reported, the thallium stress test was positive (Table 1). In contrast, in patients seen with syncope or arrhythmias, neither stress test demonstrated ischemia. The positive stress tests in this group were found only in patients in whom ventricular tachycardia developed at maximum exercise (Table 2). Two of our patients were seen with angina, with ischemia detected by stress test. To our knowledge, our patient seen with syncope represents the first such patient in whom a thallium stress test demonstrated reversible ischemia.

For patients with these anomalies, the operative procedure chosen depends on the mechanism of ischemia. In theory, this anomaly can be associated with an acute origin of the anomalous vessel causing a slitlike orifice and ostial obstruction during exercise [8, 36]. Alternatively, ischemia can be caused by compression of the anomalous artery between the great vessels during exercise [7, 38]. In the first instance, a procedure to enlarge the ostium should relieve ischemia. Such an aortoplasty has been performed in 8 patients with anomalous LMCAs (Table 3). All were symptomatic, and all were relieved of symptoms. Follow-up ranged to 9 years, and five vessels were proved patent by postoperative angiography. In 6 patients, the anomalous ostium was relocated so that it originated from the LAS [21, 26]. In the other 2 patients, the orifice was simply enlarged to compensate for the acute angle of takeoff [6, 22].

Although this operation has yielded good results, it has limitations. First, in some patients, there is no acute takeoff of the anomalous vessel, and an ostioplasty would not be an appropriate procedure. Second, if a component

Table 3. Anomalous Left Main Coronary Artery Treated Surgically by Aortoplasty

Reference	Year	Age (yr)	Sex	Symptoms	Procedure	Associated Coronary Artery Disease	Follow-up	
							Length	Result
Cheitlin et al [6]	1974	14	M	Exertional syncope	Aortoplasty	Absent	9 yr	Asymptomatic aortic insufficiency, angiographically patent left main coronary artery
Mustafa et al [26]	1981	12	M	Exertional chest pain	Aortoplasty	Absent	2 mo	Angiographically patent left main coronary artery
							3 yr	Asymptomatic clinically
		32	F	Exertional chest pain, shortness of breath	Ascending aortic replacement, aortic valve replacement	Absent	2 yr	Stress test normal
		13	M	Exertional chest pain, exertional syncope	Aortoplasty	Absent	No data	No data
Donaldson et al [21]	1983	. . .	M[a]	Exertional chest pain	Aortoplasty	Absent	. . .[a]	. . .[a]
		. . .	M[a]	Exertional chest pain	Aortoplasty	Absent	. . .[a]	. . .[a]
		. . .	M[a]	Exertional chest pain	Aortoplasty	Absent	. . .[a]	. . .[a]
Grey et al [22]	1984	33	F	Nonexertional chest pain	Aortoplasty	Absent	No data	No data

[a] Patients in this series were 15, 21, and 32 years of age. They could not be identified individually. Follow-up ranged from 10 to 24 months. There were no clinical symptoms, and postoperative angiography showed a patent left main coronary artery in all 3 patients.

Table 4. Reported Surgical Intervention for Anomalous Left Main Coronary Artery[a]

Reference	Year	Age (yr)	Sex	Symptoms	Grafts	Associated Coronary Artery Disease	Follow-up Length	Follow-up Result
Sachs et al [27]	1977	20	M	Ventricular fibrillation	RSVG/left main	Absent	5 mo	Angiographically patent vein graft; stress test normal
Murphy et al [28]	1978	12	F	Syncope	RSVG/LAD	Absent	1 yr	Angiographically patent vein graft
Liberthson et al [17][b]	1983	54	F	Chest pain at rest	RSVG/LAD, circumflex	Absent	1 yr	Angiographically patent vein graft
Ishikawa and Brandt [4]	1985	58	M	Angina	No data	Present	No data	No data
		73	M	Angina	No data	Present	No data	No data
Iskandrian et al [23]	1986	67	M	Angina	RSVG/LAD, circumflex, right coronary artery	Present	8 wk	Normal thallium stress test

[a] This table includes saphenous vein bypass grafting only. [b] In 1979, Liberthson and colleagues [24] described 2 patients who underwent coronary artery bypass grafting for refractory angina with this anomaly without follow-up.

LAD = left anterior descending coronary artery; RSVG = reverse saphenous vein graft.

of ischemia is caused by compression of the anomalous artery between the great vessels, an ostioplasty alone will not completely relieve ischemia. Third, detachment of the intercoronary commissure necessary during this procedure can cause aortic insufficiency [7]. Finally, there is potential for rapid progression of atherosclerosis at the ostium of the instrumented vessel.

An alternative procedure for this anomaly is CABG with either RSVGs or IMA grafts. This procedure has been performed with RSVGs in 11 patients, 6 with an anomalous LMCA and 5 with an anomalous RCA. The 6 patients with an anomalous LMCA all had relief of symptoms after the operation with follow-up to 1 year (Table 4). Two patients were seen with abnormal stress tests that reverted to normal, and repeat catheterization in 3 patients showed patent vein grafts. Five patients underwent operation for an anomalous RCA using an RSVG to the RCA at the base of the right atrium (Table 5). All patients had relief of symptoms with follow-up to 39 months. Stress tests in 2 patients reverted to normal.

These limited results with RSVG CABG for an LMCA originating from the right aortic sinus or an RCA originating from the LAS appear good. However, long-term results may be less favorable. Reverse saphenous vein

Table 5. Reported Surgical Intervention for Anomalous Right Coronary Artery

Reference	Year	Age (yr)	Sex	Symptoms	Grafts	Associated Cardiac Disease	Follow-up Length	Follow-up Result
Kimbiris et al [30]	1978	30	M	Ventricular fibrillation	No data	Absent	No data	No data
Keren et al [36]	1982	60	M	Angina	No data	Present	No data	No data
Bloomfield et al [8]	1983	65	M	Angina	Reverse saphenous vein graft/right coronary artery	Absent	2 mo	Stress test normal, no ischemia
Brandt et al [34]	1983	35	M	Myocardial infarction, ventricular fibrillation	Reverse cephalic vein graft/right coronary artery	Absent	9 mo	Stress test normal, no symptoms
Bett et al [35]	1985	29	M	Syncope	Reverse saphenous vein graft/right coronary artery	Absent	39 mo	Running 128 km/wk without symptoms

grafts to minimally diseased vessels show a patency rate similar to that of grafts placed to stenosed arteries, but with acceleration of atherosclerosis in the native vessel [39, 40]. Reverse saphenous vein grafts to nonatherosclerotic vessels have achieved poor results. Late follow-up of such grafts placed to correct major coronary anomalies shows one third of the grafts occluded, with the majority having either aneurysmal dilation or stenosis at 6 months [41]. Late closure of grafts to major vessels in young patients without collateral channels can have severe consequences.

The IMA was used previously by Moodie and colleagues [25] for an anomalous LMCA, and our 2 patients constitute the fourth and fifth such applications of IMA CABG. Our use of the right IMA to bypass the RCA is the first such reported instance of which we are aware. All the patients in the series of Moodie and associates were symptomatic preoperatively, and all were relieved of symptoms by the procedure. These results combined with our own suggest a good short-term outcome for this procedure. Long-term patency of IMA grafts exceeds that for RSVGs. In minimally diseased vessels, the patency rate for the IMA graft is better than that for the RSVG, and there is less chance of progression of proximal disease in the native vessel [39]. Patency rates achieved by Laborde and associates [42] with native subclavian artery grafts to treat major coronary anomalies suggest that arterial grafts will remain open when grafted to nondiseased arteries.

We propose that a patient found to have an anomalous main coronary artery coursing between the great vessels be treated in the following manner. Patients less than 30 years of age should undergo an operation because of the high incidence of sudden death as the initial presentation in younger patients. For patients more than 30 years of age, the presenting symptoms are relevant. Patients with syncope should have an operation regardless of the results of stress testing. Patients with chest pain should undergo angiography to evaluate indications for a cardiac operation, and if such indications are present, the operation should include CABG of the anomalous system. If the angiogram shows no other vessels needing bypass grafting, the anomaly should be bypassed only if thallium stress testing shows reversible ischemia. If the thallium stress test is negative, the patient can be observed, as sudden cardiac death is less likely in older patients. If the patient is asymptomatic, he or she can either be observed or undergo thallium stress testing with therapy dependent on the presence or absence of reversible ischemia. We believe the procedure of choice for this anomaly, when operation is necessary, is CABG with the ipsilateral IMA grafted to the anomalous coronary system.

Questions regarding CABG with the IMA as a procedure for this anomaly remain unanswered. (1) Should patients with an anomalous LMCA undergo a separate graft to the circumflex system? (2) Should the anomalous vessel be ligated proximally? In patients with an anomalous LMCA, we recommend bypass grafting of the circumflex system because compression of the left coronary system can occur distal to the bifurcation of the LMCA. We suggest an RSVG be used in preference to the right IMA graft to bypass the circumflex coronary artery because of the difficulty encountered at repeat sternotomy when a right IMA graft has been placed to the left coronary system, and because of the unknown patency rate of the right IMA to the circumflex system. In young patients, in whom long-term results are unknown, a repeat sternotomy must be considered a possible future event. At present, there is insufficient knowledge of the pathophysiology of graft closure to determine whether the proximal anomalous vessel should be ligated. Our current practice is to ligate an anomalous RCA but leave an anomalous LMCA patent.

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CORRESPONDENCE

Removal of Guidewire Fragment

To the Editor:

We read with interest the report of Proctor and Koch [1] regarding the removal of a guidewire fragment from a coronary artery. As they have noted, such case reports are rare in the literature; therefore, we wish to add an additional case.

A 46-year-old man with angina and a positive stress test underwent a cardiac catheterization. A 60% stenosis was present in the mid-anterior descending coronary artery; after the acute marginal branch, the right coronary artery was 98% obstructed. A guidewire was passed across the right coronary lesion; however, it could not be crossed with a 3.0-mm angioplasty balloon. When we attempted to pull back the guidewire for its removal, the tip of the wire broke and lodged within the artery. At operation, there was a hematoma present over the right coronary artery; an arteriotomy at this point exposed the wire and it was easily removed. Saphenous vein bypass was placed at this arteriotomy; a left internal mammary artery graft was placed to the mid-left anterior descending coronary artery. Postoperative recovery was uneventful.

Given the small diameter of the steerable guidewires, the tortuosity of diseased coronary arteries, and the presence of calcific plaques, fracture of these wires may not be unexpected. Removal of the retained fragments and construction of the appropriate bypass grafts should allow the patient to tolerate this infrequent complication of percutaneous coronary angioplasty.

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Reply

To the Editor:

The report of Seifert and Auer describes a case very similar to our own. In both cases a hematoma present over the artery undergoing percutaneous transluminal coronary angioplasty indicated a perforation of that artery associated with the breakage of a guidewire.

A third case has been brought to our attention by Dr Keltai of Budapest, Hungary [1]. In his patient the fracture of the guidewire resulted in complete occlusion of the left main coronary artery and serious myocardial infarction. This was despite the administration of 10,000 units of heparin sodium intravenously before percutaneous transluminal coronary angioplasty. The patient survived after coronary bypass grafting, but with an ejection fraction of 0.35. The Hungarian experience indicates the possible serious consequences of this complication of percutaneous transluminal coronary angioplasty, and also indicates that this complication is possibly more widespread than present reports suggest.

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Holter Monitoring for Bifascicular Block After Coronary Artery Bypass Operation

To the Editor:

When bifascicular block (left anterior fascicular block in combination with right bundle-branch block) occurs in the immediate postoperative period after aortocoronary bypass operation, it would seem intuitively that the risk of postoperative complete atrioventricular block is increased. Patients with this condition should probably be monitored closely, and it has been my practice over the last 5 years to perform routinely 24-hour ambulatory electrocardiographic monitoring (Holter monitoring) in this situation before discharge. The rationale for this is simply that the Holter monitoring might show some bradyarrhythmia that has not been identified in the usual postoperative monitoring, and this in turn might lead to the decision to implant a permanent pacemaker. However, it has been my impression that the result of the Holter monitoring has rarely if ever changed the management of the patient, at least with respect to the decision regarding permanent pacing.

To further study this, over the last year I have prospectively observed 14 patients who developed bifascicular block after coronary artery bypass grafting (involving cold hyperkalemic cardioplegia without lidocaine in the solution). The group included 11 men and 3 women. In 10 of 14 patients the QRS axis was normal before operation, whereas in 4 left axis deviation was present preoperatively. One of these 4 had, at least intermittently, bifascicular block before operation. In these 4 patients the bifascicular block pattern persisted. Of the 10 remaining patients, all developed new bifascicular block that persisted for at least 1 day and in most cases longer. However, subsequently, in 8 of these 10, the abnormal left axis resolved with persistence of the right bundle branch. In 1, the right bundle-branch block resolved with persistence of the abnormal left axis, and in 1 the bifascicular block pattern persisted. Thus, of the 14 patients, only 1 had normal interventricular conduction preoperatively and persistent bifascicular block postoperatively. In all the others there was either some evidence of interventricular conduction delay preoperatively or subsequent resolution of some (but not all) of the components of the surgically-induced bifascicular block.

Holter monitoring was performed as early as the second postoperative day and as late as the 11th postoperative day (mean, 4.9 days). In no patient was there serious bradyarrhythmia noted on Holter monitoring. At least 2 patients have subsequently received permanent pacemakers. One of these patients had perioperative infarction and had a pacemaker placed several months after the operation for unclear indications. Holter monitoring five days postoperatively had shown no serious bradyarrhythmia. The other patient received a permanent pacemaker on the 17th postoperative day after the occurrence of a clinically significant bradyarrhythmia. This patient had had bifascicular block intermittently before operation. The need for this pacemaker had been suspected particularly because of the presence of alternating bilateral bundle-branch block. Nevertheless, the Holter monitoring done on day 8 had revealed no serious bradyarrhythmia.

The Holter monitoring, although it did not reveal serious bradyarrhythmia, did show complex ventricular ectopy in most patients. All but 3 patients had ventricular couplets. Three of these 11 had ventricular triplets and 2 of these 3 had short salvos of ventricular tachycardia. The prognostic importance of asymp-

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tomatic complex ventricular ectopy in the postoperative period is unknown, and this finding usually did not result in a major change in the management. (In our institution most patients receive β-blockers in the postoperative period, and often the finding of this asymptomatic complex ectopy did result in an empirical increase in the dose of the β-blocker.) In my experience, complex but asymptomatic ventricular ectopy is very common after coronary artery operation, and it is not clear that the incidence in the small group of patients under study is any different than that generally seen in this setting.

In this small group of patients with new bifascicular block after coronary artery operation, the routine use of Holter monitoring did not provide information that would be useful in deciding the need for permanent pacing.

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Assessment of Exercise Oxygen Consumption: Reply

To the Editor:

We would like to thank Drs Olsen and Weiman [1] for their insightful comments and questions regarding our study [2]. Surgical resection remains the curative procedure in the treatment of lung cancer; however, in all too many patients operation is felt to be contraindicated because of the presence of concomitant diseases. In order to minimize excessive morbidity and mortality, and yet offer a curative procedure to the widest number of patients, our laboratory and others have been examining various preoperative parameters in an attempt to improve the identification of the high-risk patient. Preoperative exercise oxygen consumption (MVo_2) represents a sensitive predictor of subsequent postoperative morbidity and mortality. As stated in our article, the sensitivity of this measurement most likely reflects the ability of maximal exercise to produce the cardiopulmonary stresses seen during and after thoracotomy. Exercise oxygen consumption corresponds to the ability of the patient to tolerate discomfort, the relative degree of fitness, and the efficacy of the pulmonary and cardiovascular systems. All these factors are recognized determinants of the postoperative course.

Olsen and Weiman ask how MVo_2 predicts complications such as infection, atelectasis, or pulmonary embolism. Many postoperative complications are directly related to the sedentary state invariably present after a thoracotomy. The patient's intolerance of discomfort, weakened physical state, and impaired ability to meet the metabolic demands of healing serve to augment and prolong this high-risk period. Thus, the lower the preoperative MVo_2, the more likely the patient will have a prolonged sedentary state and be at increased risk for morbidity and mortality.

Olsen and Weiman also ask whether patients with MVo_2 of less than 10 mL/kg/min are rejected for operation. It would be nice to have the ultimate preoperative criterion for thoracotomy; however, it has yet to be discovered. We do not deny operation strictly on the basis of MVo_2. Rather, a low MVo_2 identifies those patients requiring a more aggressive evaluation. Exactly what the low MVo_2 identifies that reflects an increased risk of morbidity/mortality is unclear, but we feel it identifies clandestine left ventricular dysfunction, or limited left ventricular reserve. As such, patients with low MVo_2 undergo further evaluation of left ventricular function in an attempt to elucidate correctable etiologies. The decision whether to proceed with operation is then left to the physician and patient. Whether a specific MVo_2 value would absolutely contraindicate operation cannot be ascertained until large standardized cooperative studies are done. We feel most physicians will accept nondisabling postoperative morbidity to cure lung carcinoma. Thus, the issue is whether MVo_2 can predict pulmonary insufficiency and mortality, and what risk of mortality is acceptable in attempting to cure a lethal condition.

Finally, we disagree that our study contrasts with that of Eugene and associates [3]. These authors found that oxygen consumption of less than 1 L/min was associated with a 75% mortality. The average MVo_2 in this group was 821 mL, and if we assume an average weight of 70 kg, this converts to 11.7 mL/kg/min. In addition, they found no correlation between pulmonary function tests and postoperative mortality.

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Adjustable Annuloplasty for Tricuspid Insufficiency

To the Editor:

I was interested in the exchange of letters [1, 2] concerning the article by Kurlansky and co-workers [3]. I have comments in two areas.

First, I would like to note that claims to "paternity" of ideas can often be amusing, but also confusing. The first description of annular constriction of an atrioventricular orifice to correct regurgitation was published in 1954 [4]. The first use of such a technique in humans was reported in 1955 [5]. While we were doing this work in Philadelphia, Borrie, unknown to us, was doing a similar procedure on sheep, in New Zealand [6]. My first public mention of this approach was in 1955, both at the Henry Ford Hospital Symposium in Detroit [7] and at the meeting of the American Association for Thoracic Surgery [5]. The original mitral pursestring technique not only introduced the concept of annular constriction or reduction (or plication), but also was adjustable from outside the cardiac chambers. With a finger in the atrium, one could estimate the degree of regurgitation and tie down the suture until the regurgitant jet could no longer be detected. This technique provided, for the first time, objective proof of the correction of mitral regurgitation, both by direct atrial and ventricular pressure tracings and by visual demonstrations using the pulse duplicator [5]. This approach became obsolete with the advent of cardiopulmonary bypass and was further superceded by the early valve prostheses.

More importantly, the use of a periannular suture as described by Alonso-Lej [1] and now by Kurlansky and co-workers [3], as in the "original" De Vega technique [8, 9], could result in a migration of the suture centripetally, creating a fibrous shelf over the orifice, or in a cutting through of the suture (like a hot wire through butter) with the suture eventually lying like a chord or bowstring across the orifice. These phenomena were observed in some of our experiences with the mitral pursestring. This may result whenever the periannular suture spans something on the

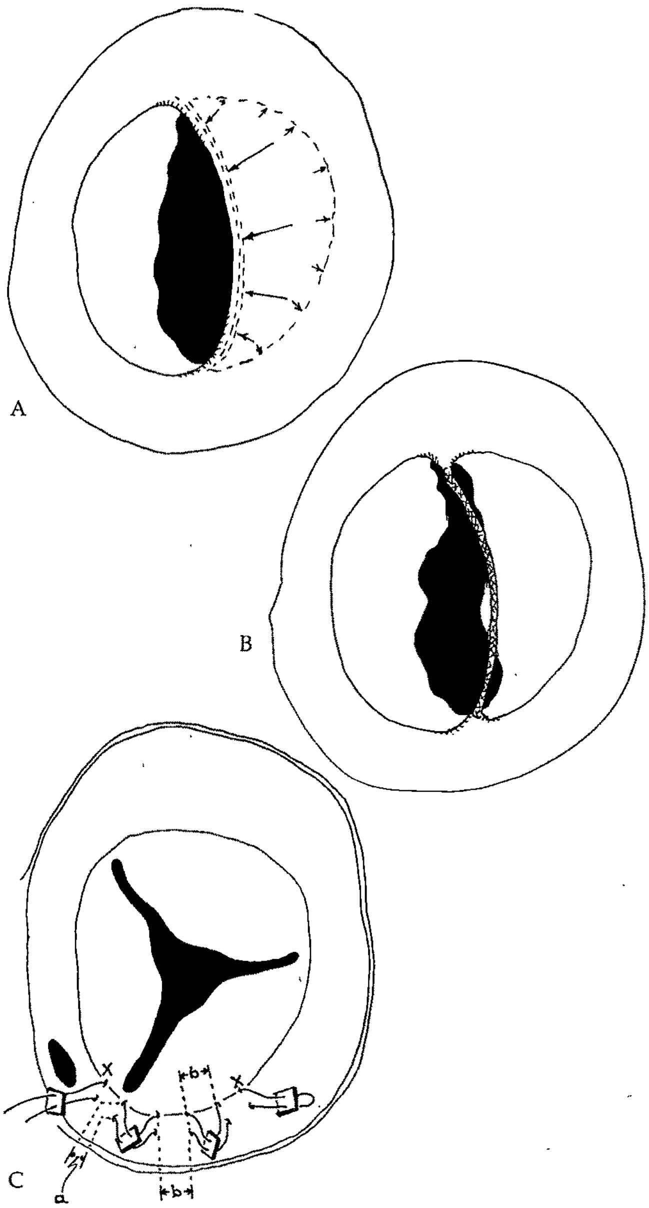

Fig 1. A. In dogs, a pursestring suture around the mitral valve sometimes resulted in formation of a crescent-shaped ledge above the valve as the suture migrated centripetally, carrying with it a film, or membrane, of scar tissue. The original location of the suture is indicated by the single dotted line; *the position of the suture after migration, by the* double-dotted line. *The* long arrows *indicate the centripetal migration of the suture; the* short arrows, *the centrifugal relaxation of the annulus with loss of the desired constricting effect. In this diagram and in (B) the septal or medial leaflet of the mitral valve is to the right, the anterior commissure is at the top. B. Also in animals, the suture (no. 5 braided Dacron or 1/8-inch cotton tape) would actually cut through and hang across the valve orifice as a chord or bowstring (the no. 5 suture consistently, the tape frequently). To try to prevent these phenomena, use of no. 5 suture material was discontinued and the medial, or septal, half of the 1/8-inch woven Dacron tape was covered with a sheath of autologous pericardium. This eliminated the problem in dogs, but not entirely in humans. C. A technique for annuloplasty described in this letter, usable in either the mitral or tricuspid valves (see text). The dimensions are quite critical. In this diagram the plication is begun just posterior to the coronary sinus and spans a segment-of-circumference opposite the posteromedial commissure of the tricuspid valve.*

order of half, or more, of the circumference. When used in the tricuspid valve, a substantial degree of pulmonary (right ventricular) hypertension would make such a failure more likely (Figs 1A, 1B).

Second, I would like to mention a simple technique that I have used since the early 1960s in both mitral and tricuspid valves. In the mitral valve it works fine alone or in combination with other maneuvers. In the tricuspid valve it has been sufficient by itself, without additional maneuvers (except, rarely, with addition of single or double commissurotomy) (Fig 1C). I do not claim "paternity" of this idea. I don't know who, if any, of the various surgeons who have performed valvular annuloplasties may have used this exact technique, or some minor variation of it. However, I don't recall ever seeing it described in print. Figure 1C illustrates the placement of "furling" stitches (ie, a continuous series of pledgeted mattress sutures, using 2-0 braided Dacron suture material and 3 × 8 × 1.5-mm Dacron or Teflon pledgets). One can make two furlings with three pledgets, or three furlings with four pledgets, as shown. I have occasionally used up to four furlings with five pledgets. One can repeat the procedure opposite any of the commissures or, indeed, one can span any short segment of the circumference. The felt (sandwiched in the folds or furls) will be infiltrated by tissue and provide a solid scar, which will prevent the suture from cutting through. Bites are taken as illustrated, one stitch on the fibrous ring itself, another about 6 mm outside the first (dimension *a* in Fig 1C), advancing 8 to 12 mm (dimension *b*) with each pair of stitches. With three furls, four pledgets, and the above dimensions, tying the suture snugly will shorten the segment-of-circumference (between the Xs) about 40% to 50%. I have found this technique effective in numerous cases, in both the mitral and tricuspid valves, when there is sufficient leaflet area to work with. The dimensions given are quite critical. Experience makes the feature of external adjustment unnecessary.

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Southern Thoracic Surgical Association Rules for Submission of Abstracts

Abstracts for papers to be presented for the 1989 Annual Meeting are now being accepted. The deadline for postmark of abstracts is May 15, 1989. An original and 1 copy should be submitted, using the official Association abstract form, to Bradley M. Rodgers, MD, Chairman, Program Committee, The Southern Thoracic Surgical Association, 111 E Wacker Dr, Chicago, IL 60601. Additional forms are available upon request from the Association.

Abstracts must summarize an original contribution not presented or accepted for presentation elsewhere. *Abstracts received after the deadline will not be considered.* The information requested at the bottom of this form must be completed indicating who is to receive the notice of acceptance or rejection and who will present the paper if accepted.

Abstracts may be submitted for the regular program, the Forum, or either. Papers selected for the Forum will be published in *The Annals of Thoracic Surgery* if they pass the usual editorial review.

Essayists are reminded that all papers accepted for presentation must be submitted in triplicate to Gordon F. Murray, MD, Secretary-Treasurer, at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation.

Abstracts frequently obscure the value of their content because they are poorly organized. It is important that methods and results be clearly defined in the abstract; general statements such as "results will be presented" are not acceptable. When a procedure or method is stated to have "advantages," those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Presentations in the regular program are limited to 10 minutes; those in the Forum are limited to 5 minutes.

In discussion of papers, the Association encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of the discussion in the form of "secondary papers" will not be welcomed.

INSTRUCTIONS FOR ABSTRACTS

The official abstract form or photocopies must be used. **Authors must indicate whether they want the abstract considered for the regular program, the Forum, or either by checking the appropriate box. Authors must also categorize the principal subject of their abstract by checking the appropriate box.**

1. Title of abstract must be completely CAPITALIZED.
2. Full names of authors must appear on the abstract, without degrees, titles, or appointments.
3. Indicate each author who is a member of the Southern Thoracic Surgical Association with an asterisk following the name.
4. Underline the name of each STSA new member (elected to membership in 1988).
5. Institution or address is to be given.
6. Abstracts must be limited to 200 words and *must be typed double-spaced.*
7. When percentages are used, the absolute numbers of derivation must be stated.
8. The body of the abstract should include:
   a. A brief statement of the purpose of the study, referring, as appropriate, to the current state of research in the field.
   b. The methods of study or experimental approach clearly defined.
   c. A summary of the results and/or conclusions of the study, including sufficient details to support those conclusions.
   d. A statement concerning the significance and implications of the work.
9. The form must be signed by the senior author attesting that the material will not be presented elsewhere if accepted for the scientific program nor published elsewhere if accepted for publication in *The Annals of Thoracic Surgery.*

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SOUTHERN THORACIC SURGICAL ASSOCIATION

Bradley M. Rodgers, MD
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Southern Thoracic Surgical Association
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THE
ANNALS OF
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Official Journal of The Society of Thoracic Surgeons
and the Southern Thoracic Surgical Association

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery,* 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Second International Symposium on Echocardiography and Doppler in Cardiac Surgery, Salzburg, Austria—May 1–3, 1989

For information on this meeting, contact G. Maurer, MD, or W. Mohl, MD, PhD, c/o Interconvention, A-1450 Vienna, Austria; or telephone 43-1-2369-2641 (telex, 11-18-03; facsimile, 43-1-2369-648).

Tenth Annual Scientific Session of the North American Society of Pacing and Electrophysiology, Toronto, Ontario, Canada—May 4–6, 1989

This meeting is accredited for credit hours in category 1 of the Physician's Recognition Award of the AMA, and application has been made to the Massachusetts Nurses Association for approval of contact hours. For information on this meeting, contact NASPE Registration, 13 Eaton Court, Wellesley Hills, MA 02181; or telephone (617) 237-1866.

Sixty-ninth Annual Meeting of The American Association for Thoracic Surgery, Boston, Massachusetts—May 8–10, 1989

For information on this meeting, contact AATS, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Vascular Surgery 1989, New York, New York—May 18–20, 1989

This symposium is cosponsored by the Long Island Vascular Clinic; the Long Island Jewish Medical Center; and the Postgraduate Institute for Medical and Dental Education, the Health Sciences Center, and the School of Medicine, State University of New York at Stony Brook. The symposium is accredited for 24 hours in category 1 from the Accreditation Council for Continuing Medical Education and the AMA. For information, contact Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042; or telephone (718) 470-8650.

First International Symposium on Heart Failure: Mechanisms and Management, Jerusalem, Israel—May 21–25, 1989

This meeting is sponsored by the Israel Heart Society. For information, contact the Secretariat, First International Symposium on Heart Failure, PO Box 50006, Tel Aviv 61500, Israel; or telephone (03) 654571 (telex: 341171 KENS IL; facsimile; 972-3-655674).

Heart Surgery 1989: Third International Symposium on Cardiac Surgery, Rome, Italy—May 29–June 2, 1989

For information on this meeting, contact the Organizing Secretariat, Assistenza Internazionale Servizi di Congresso, Viale Parioli 2, Rome 00197, Italy.

General Thoracic Surgery, Toronto, Canada—June 1–2, 1989

For information on this meeting, contact Continuing Education, Faculty of Medicine, Medical Sciences Building, University of Toronto, Toronto, Ontario, M5S 1A8, Canada; or telephone (416) 978-2718.

Eighteenth Annual Society of Critical Care Medicine Educational and Scientific Symposium, New Orleans, Louisiana—June 5–9, 1989

For information on this meeting, contact the Society of Critical Care Medicine, 251 East Imperial Highway, Suite 480, Fullerton, CA 92635; or call (714) 870-5243.

First International Workshop on Cardiomyoplasty, Paris, France—June 6–8, 1989

This meeting is sponsored by Medtronic. For information on this meeting, contact Convergences, 16 Rue Jean-

Jacques Rousseau, F 75001 Paris, France; or telex 216911 F (facsimile, 33-1-40130231).

International Symposium on Surgery for Heart Valve Disease, London, United Kingdom—June 12–16, 1989

This symposium is sponsored by Baxter Edwards CVS Division, Carbomedics, Medtronic, Pergamon Press, Inc, Shiley, St. Jude, and USCI International, and will focus on material and designs of replacement heart valves. The symposium is accredited for up to 30 hours of category 1 of the Physician's Recognition Award of the AMA. For information, contact the Symposium Secretariat, Conference Associates HVD, Congress House, 55 New Cavendish St, London W1M 7RE, United Kingdom; or telephone 01-486-0531 (telex: 934346 CONFAS G; facsimile: 01-935-7559).

International Society for Cardiovascular Surgery/Society of Vascular Surgeons, New York, New York—June 18–21, 1989

For information on this meeeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Western Thoracic Surgical Association, Monterey, California—June 21–25, 1989

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Surgery of the Airways, Boston, Massachusetts—July 17–18, 1989

This course is sponsored by the General Thoracic Surgical Department of the Massachusetts General Hospital and the Harvard Medical School Department of Continuing Education. The course is accredited for 16 hours in category 1 of the Physician's Recognition Award of the AMA. For information contact Harvard Medical School Department of Continuing Education, PO Box 825, Boston, MA 02117; or telephone (617) 732-1525.

Nineteenth World Congress of The International Society for Cardiovascular Surgery, Toronto, Ontario, Canada—September 5–9, 1989

For information on this meeting, contact XIX World Congress, ISCVS Administrative Offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Twenty-fifth Annual Meeting of The Society of Thoracic Surgeons, Baltimore, Maryland—September 10–13, 1989

For information on this meeting, contact George C. Kaiser, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Thirty-eighth Annual Meeting of The Scandanavian Association for Thoracic and Cardiovascular Surgery and The Scandanavian Society for Extracorporeal Technology, Aarhus, Denmark—September 13–16, 1989

For information on this meeting, contact the Secretary of the Congress Committee SATCVS/SCANSECT, Chr. Mouritzen, MD, Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus-Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

National Conference on Pediatric Trauma, Ann Arbor, Michigan—September 20–23, 1989

This meeting is sponsored by the University of Michigan Medical School, the Kiwanis Pediatric Trauma Institute, and the New England Medical Center. The meeting is accredited for 20 hours in category 1 of the Physician's Recognition Award of the AMA. For information contact Debbie DeSmyther, Program Assistant, Office of Continuing Medical Education, Towsley Center-Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; or telephone (313) 763-1400.

Sixth World Congress of Bronchoesophagology, Tokyo, Japan—October 15–18, 1989

This meeting is sponsored by the Organizing Committee of the Sixth World Congress of Bronchoesophagology, the Japan Broncho-esophagological Society, and the Foundation for Advancement of International Science under the auspices of the International Bronchoesophagological Society. For information, contact the Secretariat of the Sixth World Congress of Bronchoesophagology, c/o Japan Convention Services, Inc, Press Center Bldg, 2-2-1 Uchisaiwaicho, Chiyoda-ku, Tokyo 100, Japan; or telephone 03-508-1213 (telex: J33104; facsimile: 03-508-0820).

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association, Phoenix, Arizona—November 9–11, 1989

For information on this meeting, contact Gordon F. Murray, MD, Southern Thoracic Surgical Association, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 130 Madison Avenue, New York, NY. All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words. There is an additional fee of $13.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad.

SITUATIONS AVAILABLE

Cardiovascular and thoracic surgeon experienced in cardiac surgery as well as general thoracic surgery needed to join the practice of an established thoracic and cardiovascular surgeon in the Los Angeles County/South Bay area. Send curriculum vitae and details of experience.

Please respond to A-907, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to A-101, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic/vascular surgeon: B/C in general and thoracic surgery. Minimum two years of practice experience. Very active private three-surgeon practice. Located in western Pennsylvania. Salary leading to full partnership. Excellent benefits. Detailed CV must accompany response. All replies treated confidentially.

Please respond to A-107, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon, BC/BE, recent graduate, to join 3-man group for private practice in 500-bed teaching hospital, Great Lakes area, currently active in cardiac procedures. Practice includes open heart, thoracic, and vascular and pacemaker cases. Replies kept confidential. Send CV, list of cases, and references.

Please respond to A-108, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular surgeon wanted to join a 2-man group in an established practice in the Southeast. Would prefer a recent graduate, but all applications considered. Generous salary leading to partnership. Practice includes all aspects of adult cardiac, thoracic, and vascular surgery. Send curriculum vitae with experience, recommendations, and photograph.

Please respond to A-110, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae, photograph, and names of references.

Please respond to A-111, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Faculty position: The Division of Thoracic and Cardiovascular Surgery, Southwestern Medical School of the University of Texas Southwestern Medical Center, is seeking an individual with strong clinical background in adult cardiovascular/thoracic surgery, along with a commitment to education and research, for a position at the assistant professor level. Must be ABTS certified or eligible.

Send complete curriculum vitae to W. Steves Ring, MD, Chairman, Division of Thoracic and Cardiovascular Surgery, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9031. An equal opportunity employer.

Cardiothoracic surgeon wanted to join busy private practice group in excellent northern Florida location.

Please respond to A-116, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon: BE/BC wanted to join progressive, established cardiovascular/thoracic surgeon in a 72-doctor multispecialty group in a Big-10 University community of 100,000 with superb cultural advantages. Initial guarantee and fringes with early associateship. Subsequent income based on productivity.

For confidential consideration, please submit curriculum vitae to A-117, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular thoracic surgeon to join a multisurgeon private practice in the Midwest. Must be board eligible or certified. Must have expertise and experience in all aspects of adult cardiac and thoracic surgery. Generous compensation/future partnership. Send curriculum vitae outlining surgical experience, training, and references.

Please respond to A-118, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon needed to join established southern California practice. Superb salary, benefits, and lifestyle. Please send curriculum vitae.

Please respond to A-126, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

The Division of Thoracic and Cardiovascular Surgery, Department of Surgery, at the University of Maryland is seeking a cardiothoracic intensivist to work in a cardiac surgery ICU. The successful candidate must be board eligible/board certified in Surgery, Internal Medicine, or Anesthesiology with special eligibility or certification in Critical Care. Salary commensurate with experience. Experience in clinical research helpful.

Applicants should submit a current curriculum vitae and three professional references to Joseph S. McLaughlin, MD, Professor and Head, Thoracic and Cardiovascular Surgery, University of Maryland Professional Building, c/o Suite 320, 419 W Redwood St, Baltimore, MD 21201. AA/EOE.

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland, OR 97213-2282.

Thoracic-vascular surgeon: Board certified or eligible surgeon wanted to join very active noncardiac thoracic vascular practice in small community with referral base of approximately 125,000. Salary leading to full partnership. Advantages of living in a small community in eastern Ohio less than one hour from large desirable metropolitan area. Will also consider applicants primarily interested in vascular surgery. Respond with curriculum vitae.

Please respond to A-125, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon: The University of Maryland, Department of Surgery, is seeking a Cardiothoracic Surgeon at the Assistant Professor level, effective July 1, 1989. Successful candidates should have special expertise in pediatric cardiothoracic surgery and transplantation with a major commitment to an academic career effective July 1, 1989. Excellent University fringe benefits package and salary commensurate with experience.

Please send curriculum vitae and three professional references to Joseph S. McLaughlin, MD, Professor and Head, Division of Cardiovascular and Thoracic Surgery, Department of Surgery, University of Maryland Professional Building, Suite 320, 419 W Redwood St, Baltimore, MD 21201. AA/EOE.

Cardiovascular and thoracic surgeon BC/BE wanted for established 3-man group in Northeastern Ohio. Adult cardiac, vascular, and thoracic experience needed. Please send curriculum vitae.

Please respond to A-124, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV and photo.

Please respond to A-122, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon, board certified or eligible, needed to join a busy adult cardiac surgery practice. Opportunity to join two cardiac surgeons performing over 400 open heart procedures annually in a competitive environment in south central Pennsylvania.

Please respond with curriculum vitae, clinical experience, and references to Robert A. Albus, MD, 650 N Twelfth St, Lemoyne, PA 17043, or call (717) 763-7551.

Postresidency clinical associate position available in cardiopulmonary surgery with University-based large service starting July 1989 or January 1990 for 1 to 2 years. Up to 25% research opportunity option available. Complete training in cardiopulmonary surgery desirable. Must be a graduate of an American medical school and eligible for full licensure in Oregon.

Please respond to Albert Starr, MD, 9155 SW Barnes Rd, Suite 240, Portland, OR 97225.

Cardiothoracic surgeon to join established group in northwest Indiana (very near Chicago). Excellent salary. Please respond with curriculum vitae.

Please respond to A-121, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon wanted for an established practice in Dallas, TX. Candidate must be board certified or eligible.

Please send curriculum vitae to Dallas Cardiovascular Surgery Associates, 7777 Forest Lane, Suite A-323, Dallas, TX 75230.

First Assistant, Cardiovascular Surgery: Excellent opportunity to join a dynamic 200-physician multispecialty clinic, located in northeastern Pennsylvania, in a challenging position as a Physician's Assistant. Outstanding noncontributory benefits and competitive salary.

Please send resume to Guthrie Clinic, Guthrie Square, Sayre, PA 18840; or telephone (717) 888-5858.

Three-man group currently performing adult cardiac, thoracic, and vascular surgery in desirable northeast location. Seeking associate leading to partnership. Candidate must be BC/BE.

Please respond to A-132, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Excellent professional opportunity for cardiothoracic surgeon to join director of new adult cardiac and thoracic surgery program in California wine country. Beautiful semirural geographical surroundings, easy access to San Francisco, desirable area for family. Send curriculum vitae, photo, references—new graduate preferred.

Please respond to A-133, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon: BE/BC, wanted to join established 3-man practice in southern California. Very busy team doing 1,000 cases/yr. Excellent location and benefits. Practice includes all aspects of adult cardiac, thoracic, and vascular surgery. Please respond with curriculum vitae and recent photograph.

Please respond to A-134, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic Surgeon: Major teaching medical center invites applications for a surgeon to develop a cardiac surgery program. Demonstrated leadership ability, previous academic responsibility, active participation in clinical cardiovascular and thoracic surgery, and a dedication to the delivery of excellent patient care are required. Previous experience in program development a strong advantage. Candidates must be board certified in cardiothoracic surgery. Salary and benefits based on experience.

Please submit curriculum vitae to Carl M. Marchetti, MD, Vice President, Medical Affairs, Jersey Shore Medical Center, 1945 Route 33, Neptune, NJ 07754.

Noncardiac thoracic and vascular surgeon needed to join well-established 1-man private practice in RI. Please submit curriculum vitae and three references.

Please respond to A-130, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular surgeon wanted to join established cardiac and thoracic surgeon to handle rapid growth in an intermountain western state. Please send curriculum vitae and summary of clinical experience.

Please respond to A-129, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic and vascular surgeon, American graduate, BE/BC, needed to join an established practice in the Southwest, specializing in adult cardiac, thoracic, and vascular surgery. Salary and fringe benefits leading to partnership. Send curriculum vitae and recent photograph.

Please respond to A-128, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

The Department of Surgery, University of California, San Francisco, is seeking an academic cardiothoracic surgeon at the Associate Professor/Professor level, for Chief of Arrhythmia Surgery at the University of California Medical Center. Applicant must be board certified in cardiothoracic surgery and have independent operating experience in adult and pediatric cardiac surgery and extensive personal experience in the surgical treatment of ventricular and supraventricular arrhythmias. The candidate must have a strong background in electrophysiological research and in surgical education. The candidate will be a full-time member of the Division of Cardiothoracic Surgery, Department of Surgery, University of California, San Francisco.

Interested individuals should submit curriculum vitae to Donald J. Magilligan, MD, Chief, Cardiothoracic Surgery, Room M-896, University of California, San Francisco, CA 94143-0118. The University of California, San Francisco, is an equal opportunity/affirmative action employer. Women and minorities are encouraged to apply.

Cardiac surgeon sought for beautiful Rocky Mountain region. 200+ cases per year in a 282-bed regional hospital. Excellent salary and benefits with bonus incentives leading to partnership after third year. Outdoor activities abound in excellent living environment. Board certified/eligible required. Please respond with curriculum vitae and references.

Please respond to A-100, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Thoracic surgeon/thoracic oncology: Full-time staff position available for highly qualified, board certified individual at major teaching institution in New York City.

Please respond to A-127, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Recently trained, board certified or eligible thoracic and cardiovascular surgeon needed to join established surgical practice in beautiful wooded deep east Texas. Charming university community. Diversified practice of pulmonary, vascular, and cardiac surgery. No pediatric open heart surgeries.

Please respond to A-131, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon wanted for busy, expanding Southeastern private group in regional medical center with university affiliation. Practice includes most aspects of adult and pediatric cardiac and thoracic surgery. Surgeon must be board eligible or certified with contemporary training. Excellent opportunity for suitable applicant.

Please respond to A-135, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

The Division of Cardiothoracic Surgery at the Albany Medical College is seeking two academic cardiac surgeons with excellent clinical skills and proven records of accomplishment in clinical and laboratory research demonstrated by publications and extramural grant awards. The successful candidate must be certified by the American Board of Thoracic Surgery and qualify for a faculty appointment in the Department of Surgery of the Albany Medical College. The Division offers a stimulating professional environment including an approved cardiothoracic residency, an active research laboratory, a well-developed practice of cardiac and thoracic surgery, and a competitive salary and benefit package. Albany Medical College is an affirmative action, equal opportunity employer.

Please send curriculum vitae and three letters of recommendation to Martin F. McKneally, MD, Division of Cardiothoracic Surgery, Albany Medical College, A-61, ME 702, Albany, New York 12208.

SITUATIONS WANTED

Cardiovascular and thoracic surgeon, 42, American, ABS, ABTS, ABVS. Eight years private practice experience. Completing overseas fellowship in heart and heart/lung transplantation July 1989. Seeks opportunity with program involved in transplant surgery. Curriculum vitae and references upon request.

Please respond to W-546, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon, mid-50's. University trained, ABS/ABTS, 14 years of extensive and highly successful solo practice in vein and IMA CABG, valve, pulmonary and vascular surgery. Experienced in starting open heart program. Strong surgical and clinical skills. Seeking private practice opportunity, either starting new program or in association with established individual or group.

Please respond to W-100, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon, 40, wishes to relocate, preferably in the Southeast. American university trained, ABS, ABTS, FACS. Private practice experience in adult cardiac, thoracic, and peripheral vascular surgery. Willing to initiate new program. Curriculum vitae and references upon request.

Please respond to W-101, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiac, vascular, and thoracic surgeon, 50, wishes to relocate. Academic background with numerous publications. Greater than 10 years private practice—set up open heart unit. CV on request.

Please respond to W-103, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon, 33, ABS certified, ABTS eligible, available July 1989. University trained with experience in IMA grafts, coronary surgery, valvular surgery. Solid exposure to complex congenital surgery and electrophysiology. Seeks private practice situation but would be delighted to accept some academic responsibilities. Prefer Mid-to-North Atlantic states or Midwest.

Please respond to W-104, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Chief resident in cardiothoracic surgery in major New York training program, finishing June 1989. Interested in private practice in Northeast. Curriculum vitae and references upon request.

Please respond to W-105, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon wishes to relocate. University trained with ABTS certification. Ten years' experience with extensive cardiac, thoracic, and peripheral vascular surgery. Would be interested in starting new program or association with group. Curriculum vitae and references available upon request.

Please respond to W-110, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiothoracic surgeon, 42, seeks relocation to Chicago area. University trained, ABTS/ABS certified, STS, FACS. Nine years private practice in Ohio, extensive experience in adult cardiac surgery, including IMA, mitral valve repair, PTCA support. Active in teaching, 22 publications. Would consider private or academic position, willing to initiate new cardiac program. Curriculum vitae on request.

Please respond to W-107, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Pediatric and adult cardiovascular surgeon, 33, board eligible, seeking staff position. Extensive training in both complex congenital and adult valve and coronary surgery. Experienced in internal mammary artery grafting. Proficient in preoperative and postoperative management of adult and pediatric patients. Curriculum vitae and references on request.

Please respond to W-108, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon looking for a position to first assist with busy cardiovascular surgeon or group. More than 10 years experience after training.

Please respond to W-109, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

General thoracic surgeon, 38, trained abroad and US, qualified as general and thoracic surgeon (foreign boards), FMGEMS, FLEX, wishes to relocate to an English-speaking country. Extensive training and experience in thoracic oncology, trauma, infections, and reconstructive surgery. Curriculum vitae and references available on request.

Please respond to W-112, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

Cardiovascular and thoracic surgeon, 51, ABS/ABTS certified, seeks group or individual practice opportunity for relocation. Trained and experienced in all facets of the field and competent in thoracic and vascular surgery. All locations considered. Available immediately. CV and references on request.

Please respond to W-111, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

FELLOWSHIPS

The Department of Surgery and Division of Cardiothoracic Surgery has immediate openings for Clinical Fellows in Adult and Pediatric Cardiothoracic Surgery.

Please respond to T. D. Ivey, MD, Division of Cardiothoracic Surgery, Department of Surgery, University Of Cincinnati Medical Center, 231 Bethesda Avenue, Cincinnati, OH 45267-0558.

Fellowship in thoracic and cardiovascular surgery available July 1989.

Contact Dr Harold C. Urschel, 3600 Gaston Avenue, Suite 1201, Dallas, TX 75246; telephone (214) 824-2503.

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819.

Surgical fellow: Clinical fellowship position available in adult and pediatric cardiothoracic surgery. Large volume of cases. NJ license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Dept of Surgery, Deborah Heart & Lung Center, Browns Mills, NJ 08015.

Clinical fellowship in adult cardiothoracic surgery available. Excellent stipend and fringe benefits.

Please send curriculum vitae to Eldred D. Mundth, MD, Bryn Mawr Medical Building, North, 830 Old Lancaster Road, Bryn Mawr, PA 19010.

Cardiac surgery research fellowship: Research fellowship in cardiac surgery available for 1–2 years beginning in July 1989. Major projects include laboratory and clinical research in cardiomyoplasty, the use of skeletal muscle for cardiac assist. Position also provides access to leading thoracic surgery training program. Salary is negotiable.

Contact James D. Sink, MD, The Emory Clinic, Section of Cardio-thoracic Surgery, 1365 Clifton Road, NE, Atlanta, GA 30333; (404) 321-0111, Extension 3616.

Fellowship, thoracic surgical oncology: Position available July 1989 in the Department of Thoracic Surgery and Oncology at Roswell Park Memorial Institute, Buffalo, NY. Training will focus on diagnosis, treatment, and research in the intrathoracic malignancies, especially lung cancer. Areas of interest include surgery, chemotherapy, immunology, and immunotherapy. Applicants must have had at least 3 years of approved residency training in the US.

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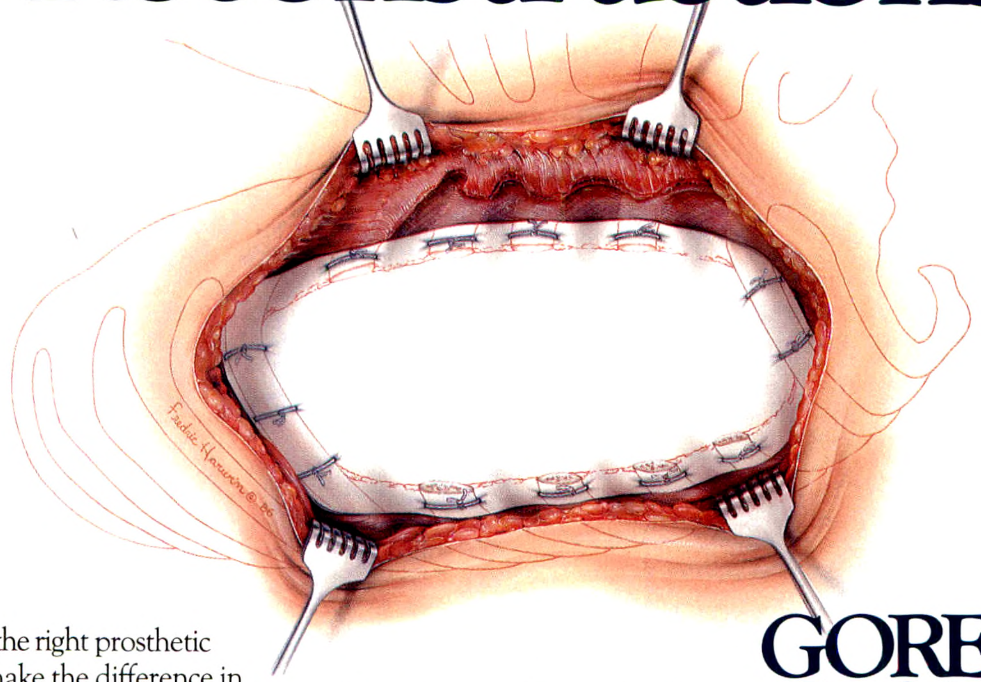

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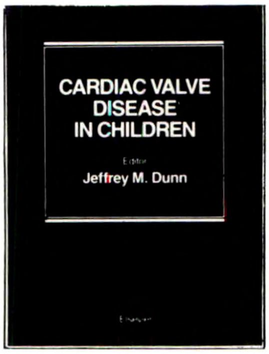

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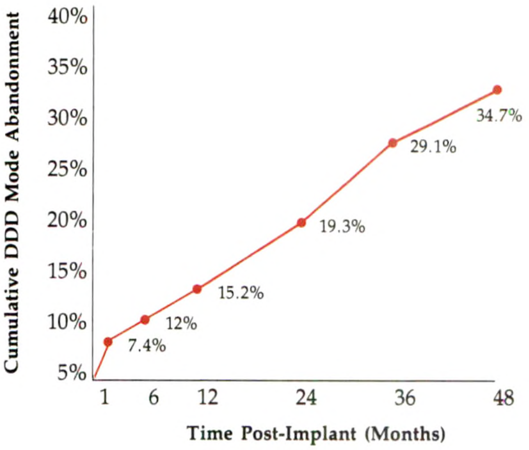

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[1] Atrial arrhythmias, loss of atrial sensing, sinus node dysfunction, atrial lead complications, chronotropic incompetence.

[2] Klementowicz, *PACE*, 10(2):409, Mar-Apr 1987.

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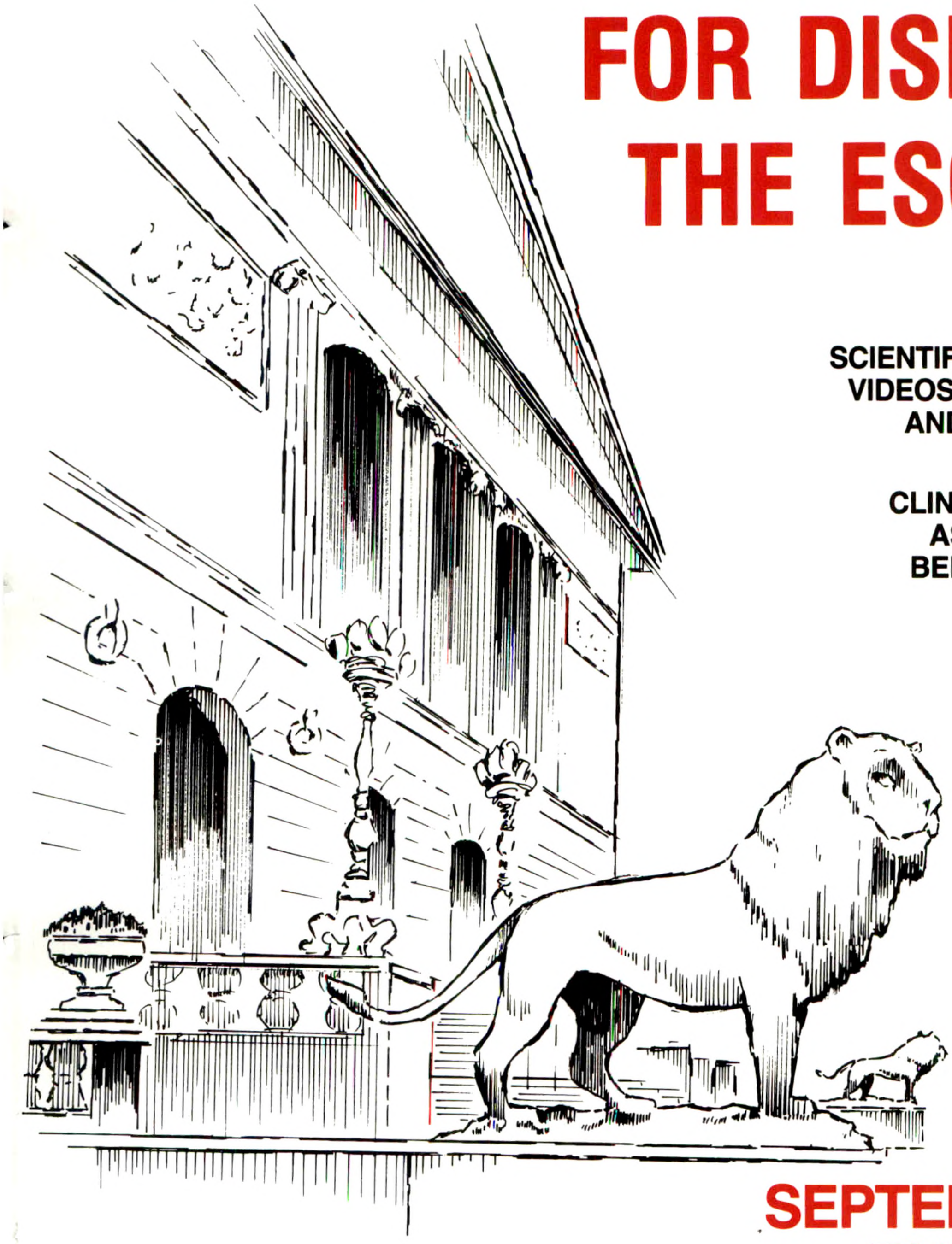

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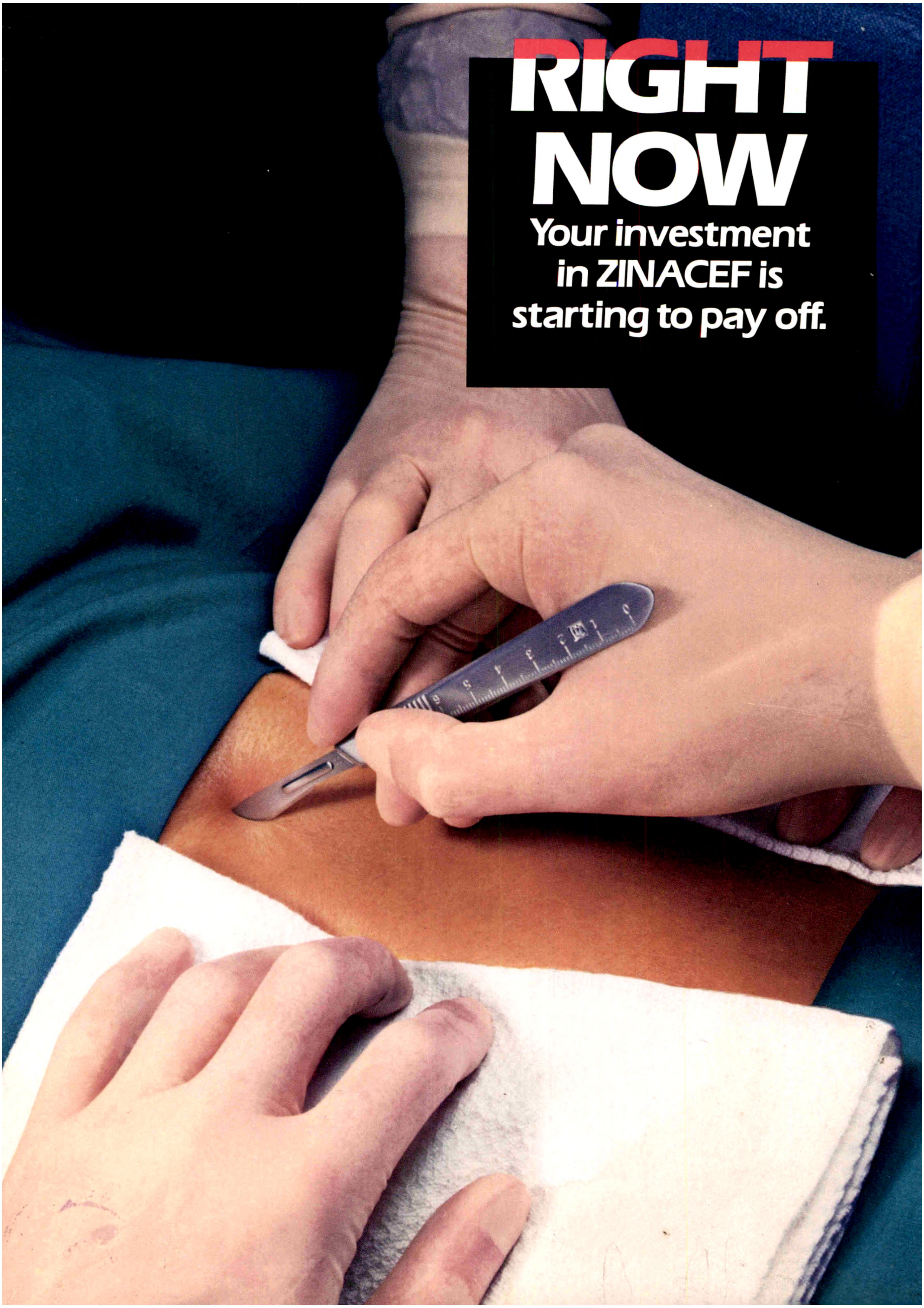
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2. Haley RW, White JW, Culver DH, et al: The financial incentive for hospitals to prevent nosocomial infections under the prospective payment system. *JAMA* 1987;257:1611-1614.

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The perioperative use of ZINACEF has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that ZINACEF therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: ZINACEF® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics) therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *C difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although ZINACEF® rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of ZINACEF should be reduced in patients with transient or persistent renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of ZINACEF may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Interference with Laboratory Tests: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving ZINACEF.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since ZINACEF is excreted in human milk, caution should be exercised when ZINACEF is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: ZINACEF® is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with ZINACEF and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence was seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients) and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

HOW SUPPLIED ZINACEF® is a dry, white to off-white powder supplied in vials and infusion packs.

Each vial contains cefuroxime sodium equivalent to 750 mg, 1.5 g, or 7.5 g of cefuroxime. ZINACEF in the dry state should be stored between 15° to 30°C (59° to 86°F), and protected from light.

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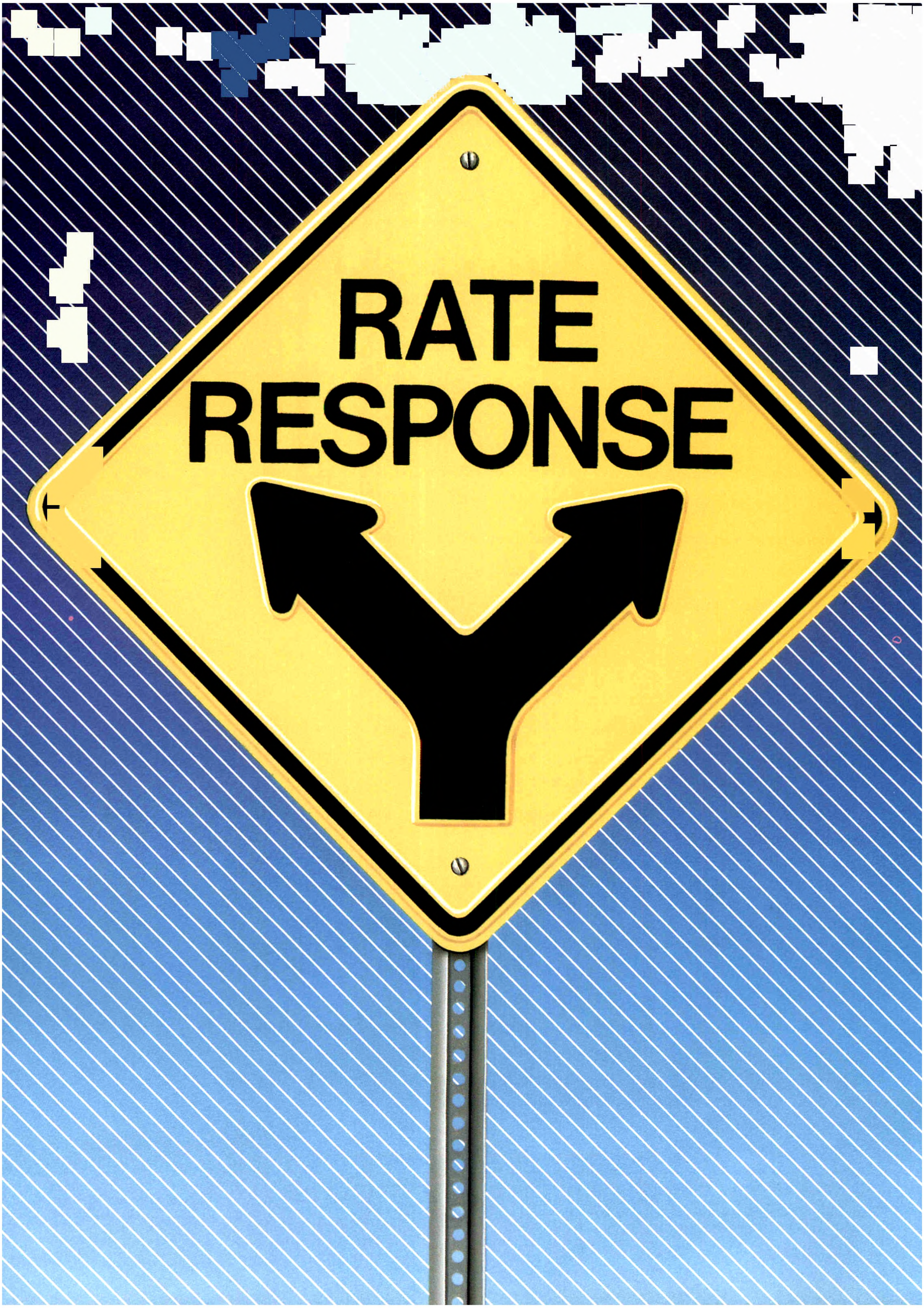
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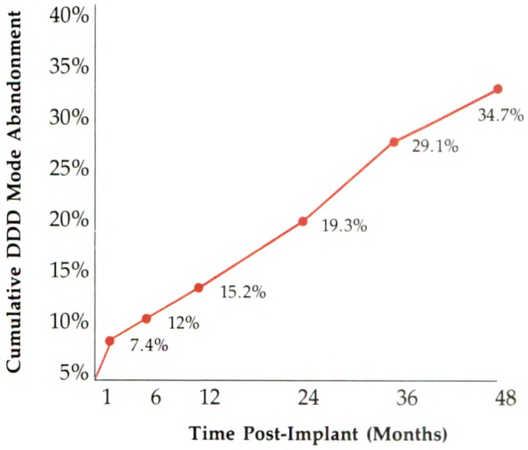

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Footnotes/References
[1] Atrial arrhythmias, loss of atrial sensing, sinus node dysfunction, atrial lead complications, chronotropic incompetence.
[2] Klementowicz, *PACE*, 10(2):409, Mar-Apr 1987.

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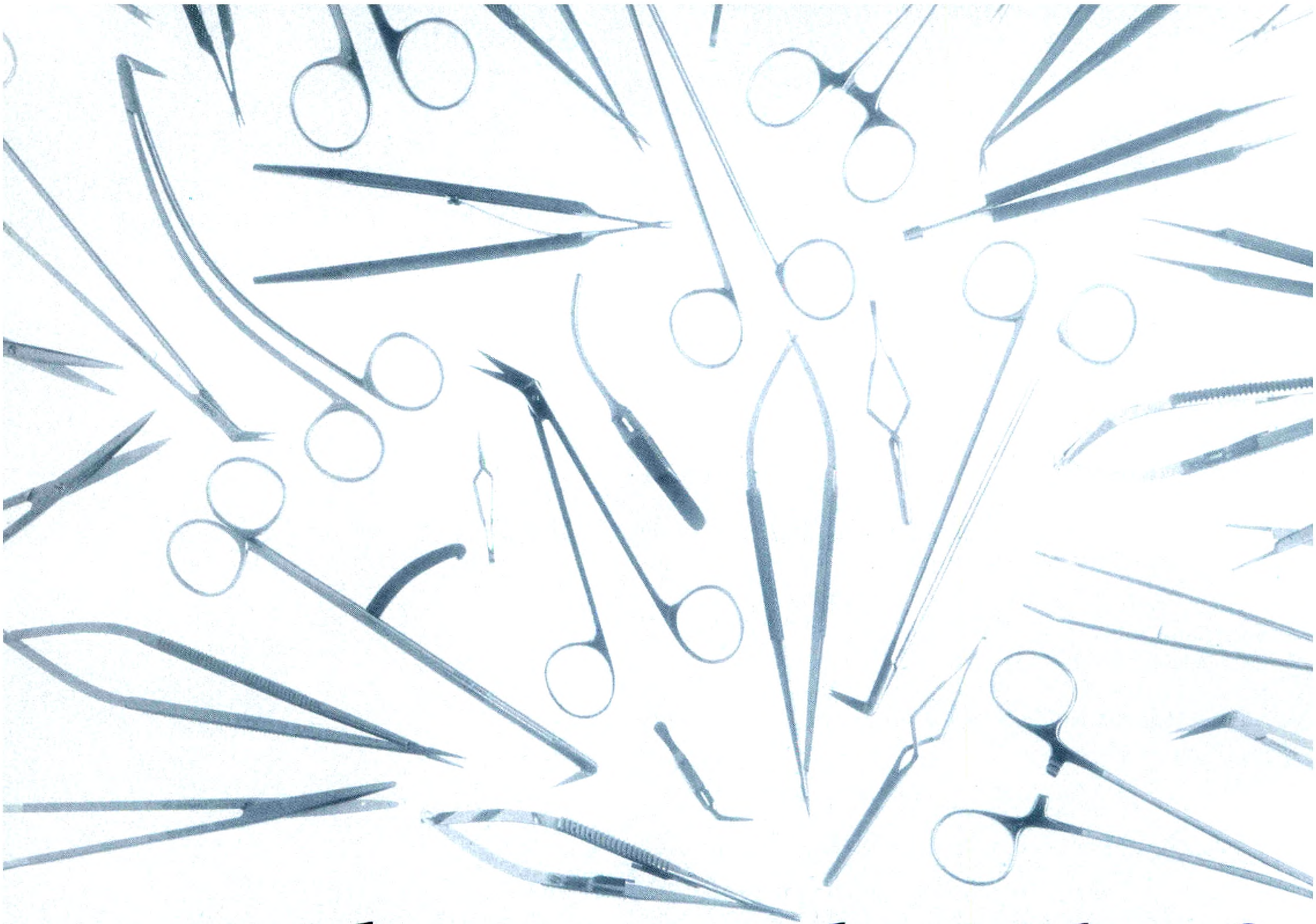

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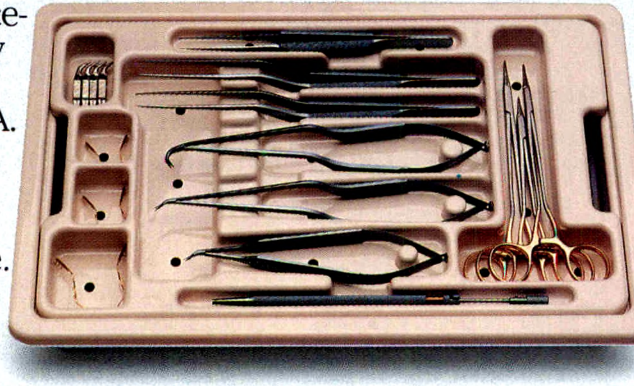

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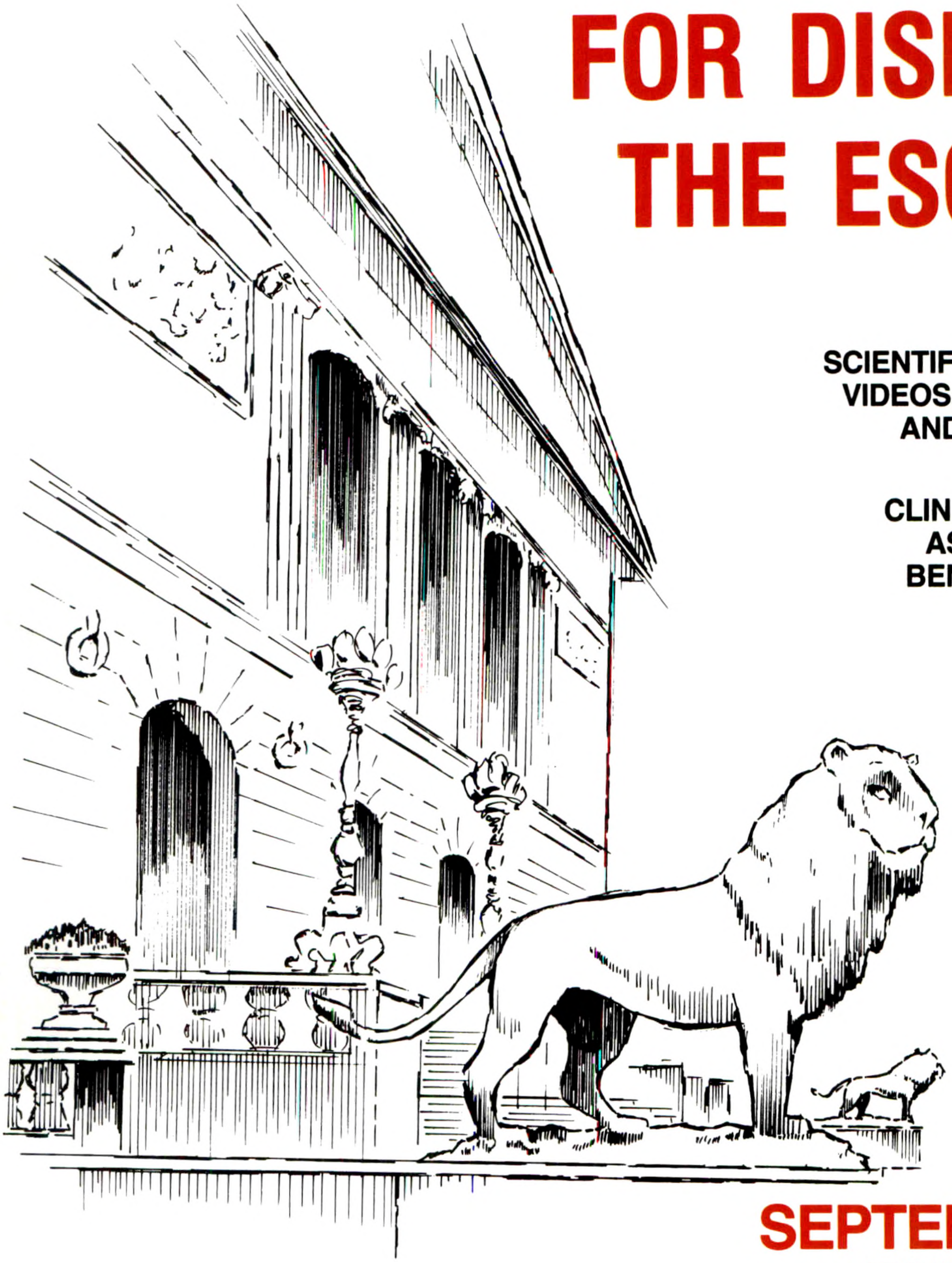

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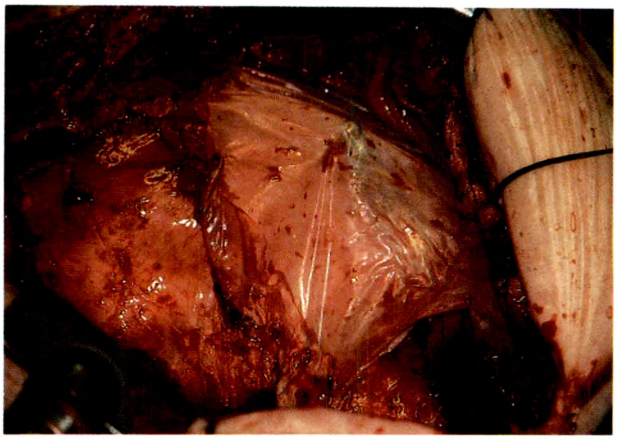

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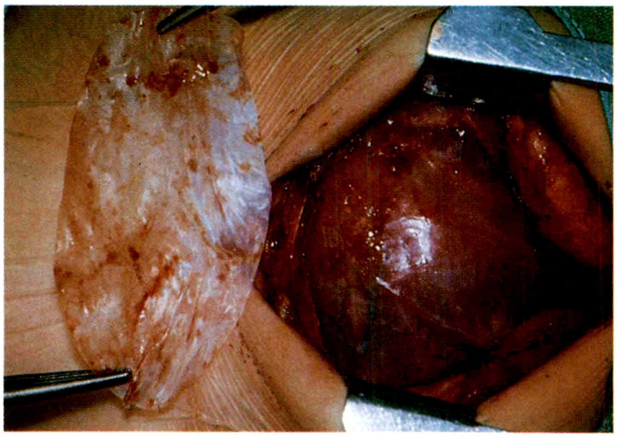

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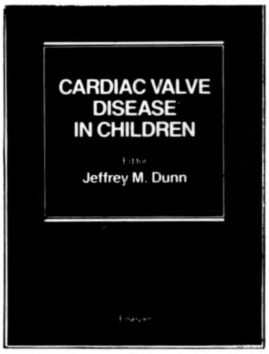

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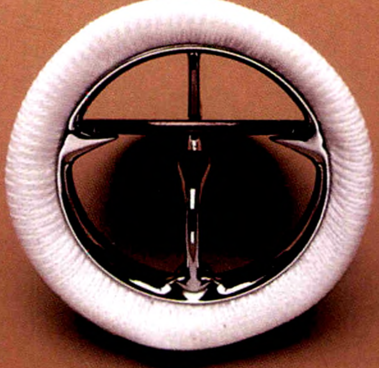

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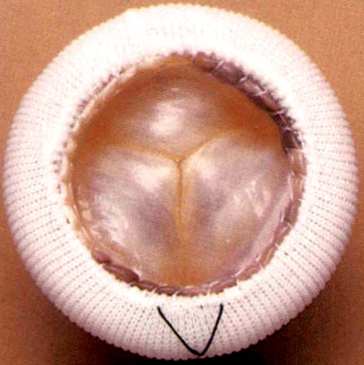

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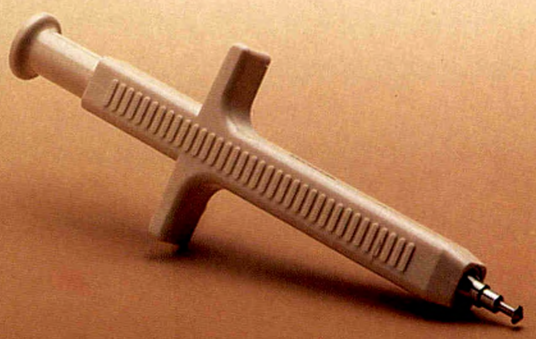

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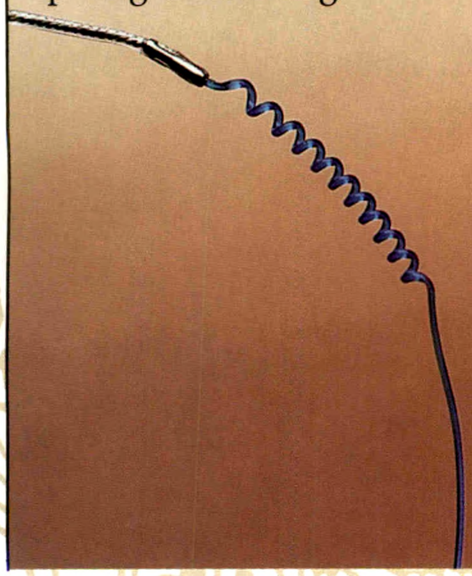

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CORONARY HEART DISEASE IN THE ELDERLY

Working Conference on the Recognition and Management of Coronary Heart Disease in the Elderly, held September 4-6, 1985, at the National Institutes of Health, in Bethesda, Maryland.

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This comprehensive work assesses our current knowledge about atherosclerotic coronary heart disease in the elderly. Research specialists survey the latest findings in the pathophysiology, epidemiology, diagnosis, prevention, and management of coronary heart disease in the geriatric population. The result is a book that provides cardiologists and gerontologists with a wealth of clinical information, including better outlines and goals for future research.

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More Attempts to Monitor Quality Assurance for Myocardial Revascularization

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The paper in this issue by Edwards and associates [1] is timely and illustrates a continuing, vexing problem that I am afraid will be difficult to overcome. No body of physicians is more keenly aware of the public attention that has been placed on the widely publicized Health Care Financing Administration (HCFA) outcome data than surgeons who perform myocardial revascularization procedures [2, 3]. Indeed, certain cardiac surgeons and institutions have seen fit to publicize their mortality statistics for Medicare patients undergoing coronary artery bypass grafting (CABG) in transparent attempts at self-aggrandizement. Unfortunately, the American population, especially frightened individuals with heart disease, cannot be expected to appreciate the chicanery that lies behind such powerful advertisements. Cardiovascular surgeons learn early in their training that one of the key factors responsible for high or low mortality rates is patient selection. I do not want to sound too cynical, but when I see a hospital advertising on television or in *The Wall Street Journal* that they have no deaths after coronary operations, it makes me question the indications for operation at that institution.

The obvious missing link that could transform these meaningless "raw" CABG mortality rates into rational assessments of quality of care is a satisfactory data base containing all pertinent patient risk factors [2]. These data, if available, could then be used to adjust the short-term outcome statistics on the basis of preoperative risk status of the patient population at that particular institution. Then, and only then, would comparison of mortality rates between hospitals or between different surgical groups be an intelligent exercise and be expected to yield meaningful conclusions. The very limited adjustments for "case mix" in compilation of the HCFA data (age, sex, and race) are clearly inadequate.

Ideally, additional dependent outcome variables reflecting the quality of CABG should be assessed, including completeness of revascularization, use of one or more internal thoracic arteries, incidence of perioperative myocardial infarction or reoperation for hemorrhage, and long-term freedom from coronary reintervention (percutaneous transluminal coronary angioplasty or CABG). The ideal is unrealistic given the limitations inherent in the extant data collection system in most hospitals.

Although limited in scope, the current report by Edwards and associates [1] from Walter Reed Army Medical Center attempts to do just that in a practical way using a Bayesian analytical model that they developed from the Coronary Artery Surgery Study (CASS) registry data [4–6]. This represents an extension of their previous work, which developed the Bayesian conditional probability matrix internally from their own patient base [7]. In turning to an accepted "external standard of care" to derive their model, Edwards and associates believe that the calculated "observed/expected" ratios would be more indicative of broader quality standards. As intuition would predict, the CABG results at Walter Reed compared more favorably with the CASS model than they did against their internal conditional probability matrix [7]. This was a major pitfall in their previous study, as application of any standard based on one's own results is basically a self-fulfilling prophecy. (Such an approach may be valid, however, if one institution desires to examine if any real differences in outcome exist between different individual surgeons in that hospital, assuming the patient cohorts are large enough to provide meaningful samples.)

Unfortunately, Edwards and associates did not provide the actual mathematical algorithms used in their analysis so that other interested parties could have applied this model to their own patient populations. I cannot accept their previous admonition [7] that the necessary "sophisticated computer support" does not exist widely in North America. Their simplified model incorporated only seven independent variables—age, gender, ejection fraction, extent of coronary disease, previous myocardial infarction, unstable angina, and surgical priority. Reoperation, recent acute myocardial infarction (with or without lytic therapy), cardiogenic shock, and failed percutaneous transluminal coronary angioplasty were not inspected because these parameters were unavailable in the CASS registry; this limits the utility and attractiveness of employing the CASS data as a standard reference, but is understandable. Edwards and associates comment that the logistic regression equation developed by Kennedy and co-workers [4] from analysis of the larger CASS registry accomplishes the same goal, but is "difficult"; they may be correct, but others have been able to apply it constructively either in its original form or in a simplified manner [8]. Irrespective of which method is employed, only this general type of analytical approach [2] will provide meaningful information and obviate fallacious comparisons.

The goals of the report by Edwards and associates [1] are admirable and overdue; the authors should be complimented for their efforts. Parenthetically, this report emanated from a Federal hospital; a similar, but more

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comprehensive approach intended for broad application in another arm of the Federal health care delivery system—the Veterans Administration hospital system—is also currently being implemented (Grover FL, personal communication). One advantage of the Veterans Administration cardiac surgery quality assurance plan is that the dynamic nature of the process will be incorporated; ie, the changing patient substrate over time will continually be used in the model to generate observed/expected ratios. This may represent one flaw in the current investigation, as pointed out by its authors [1]. We all realize that patients undergoing operation in 1989 differ substantially from the 1975–1978 CASS registry CABG cohort; indeed, the risk status of the CASS patients is much more similar to that of patients undergoing percutaneous transluminal coronary angioplasty today [3]. Therefore, it is imperative that this dynamic, continuous change in risk factors be taken into account by whatever algorithms are employed. Apparently, according to Edwards and associates [1], introduction of temporal variables can adversely affect the validity of the Bayesian conditional probability matrix model. Therefore, perhaps appropriate time-dependent multivariate linear methods (eg, Cox model) would be preferable, as they can detect the influence of interaction terms as well as time on the dependent variable under inspection.

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Management of Subaortic Stenosis in the Univentricular Heart

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In this issue, Drs Bethea and Reynolds [1] describe, quite rightly, surgical palliation of subaortic outflow tract obstruction in univentricular hearts as problematic and difficult. The key to the short-term and long-term management of patients with this anatomy is the early recognition of the bulboventricular foramen or ventricular septal defect (VSD) as actually or potentially restrictive. Perhaps the most important determinant of the potential for subaortic stenosis is the size of the VSD relative to the aortic root. In the absence of naturally occurring pulmonary outflow tract obstruction, the VSDs tend to be relatively small compared with the size of the aortic root. Such defects are elliptical, much like a "buttonhole," and are entirely muscular. The natural history of the moderate-sized muscular VSD is that of spontaneous diminution in size, and we believe this natural tendency is accelerated by pulmonary artery banding. Imaging of the VSD can be accomplished with cross-sectional echocardiography or by selective angiocardiography.

At least in retrospect, the patient reported by Bethea and Reynolds, when catheterized at 5 years of age, already had well-established subaortic stenosis, despite a pressure gradient of only 10 mm Hg. We have shown that quite severe obstruction at the VSD in this setting may be present without any resting pressure gradient (as noted by Bethea and Reynolds) because the left ventricle can decompress through the pulmonary outflow tract. Challenging this patient with isoprenaline at the preoperative catheter study and precise imaging of the VSD perhaps would have focused attention on the "malignant" character of the VSD in this particular patient. At the time of the Fontan procedure, either the VSD could have been enlarged, or a proximal main pulmonary artery–ascending aorta connection could have been established.

Since our report in 1986 [2] we have continued to gain experience with various measures designed to relieve this form of subaortic stenosis. Currently we favor a direct approach, enlarging the bulboventricular foramen through either the right atrium or the aortic root to avoid potential damage to coronary arteries and the effects of a ventriculotomy. The aortic root is preferred if associated subvalvular stenosis must be excised as well. There are disadvantages, namely, the risk of creating heart block, the occasional anatomical difficulty in creating a defect of sufficient size, and the tendency for some defects to gradually constrict.

The technique described by Bethea and Reynolds, interposition of a valved conduit between the ventricle and the ascending aorta, was used in 3 children. In each instance we combined this with direct enlargement of the ventricular septal defect, hoping to reduce the impact of later conduit stenosis or stenosis of the VSD. Although the obstruction was relieved in each patient, we were concerned about the subtle loss of ventricular function that results from the presence of a conduit on the systemic ventricle. This is particularly important in a small child or after a Fontan repair. Consequently, although we congratulate Bethea and Reynolds on their successful result and agree that this procedure is a potential alternative for the relief of subaortic obstruction, we believe it should be used selectively.

There are several other options. Not only is creation of an aortopulmonary window proximal to the site of a pulmonary artery band difficult because of the proximity of the pulmonary valve, but it results in a relatively small communication. An easier and useful procedure is anastomosis of the proximal divided pulmonary artery to the side of the aorta, although this also may be awkward when the pulmonary artery is directly posterior to the aorta. Damage to or distortion of the semilunar valves must be avoided. In both procedures there is little risk of heart block or loss of ventricular function.

In 4 children with relatively large accessory ventricles with reasonable promise of useful function, we combined an arterial switch with a Fontan-type repair, inserting a valved conduit between the right atrium and the new right ventricle. This allowed repair of the restrictive VSD and had the additional advantage that a moderate increase in pulmonary vascular resistance was tolerated. The disadvantages included the magnitude of the operation and the use of a conduit that will eventually need replacing.

Most instances of bulboventricular foramen stenosis occur in children who required pulmonary artery banding to control excessive pulmonary blood flow in infancy. The real challenge is appropriate early management that will eliminate the effect of the subaortic stenosis and avoid the need for pulmonary artery banding. By avoiding these conditions, which would lead to myocardial hypertrophy, the potential for eventual Fontan repair is improved. The main option at present is a Norwood procedure, joining the proximal pulmonary artery to the aorta while perfusing the isolated distal pulmonary artery with a shunt [3]. A second option, described by Litwin and colleagues [4], involves pulmonary artery banding and interposition of a graft between the proximal pulmonary artery and the descending aorta. Both procedures produce a brittle postoperative physiological state which requires meticulous

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intensive care, and the final success rate, in terms of an ultimately successful Fontan procedure, is generally small but improving. It would be most rewarding to find a better solution to this problematic and difficult malformation.

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Risks of Cardiac Transplantation

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Cardiac allotransplantation is now deservedly recognized as an effective treatment for end-stage myocardial disease. Nevertheless, until the development of treatments that render the transplant recipient selectively tolerant of the donor organ while preserving the integrity of the remainder of the recipient's immune defenses, heart transplantation will remain a palliative, not a curative therapy. Like patients who have had implantation of prosthetic cardiac valves, transplant recipients are subject to the risk of a variety of hazards after transplantation.

Transplantation-related complications that have been reported include death, rejection, infection, graft atherosclerosis, neoplasia, hypertension, renal insufficiency, diabetes mellitus, osteoporosis, gallstones, pancreatitis, acquired immunodeficiency syndrome, and hepatitis, among others. On pages 650 to 654 of this issue, Greene and associates report a sophisticated nonparametric analysis of the time-related risk of death, rejection, and infection in a series of 95 patients receiving heart transplants at the Johns Hopkins Hospital over the past 5 years. This report is representative of a new focus in the literature on quantification, not mere identification, of morbidity after transplantation.

The credibility of such a quantitative analysis is clearly dependent on the completeness of follow-up surveillance, length of follow-up, frequency of observation of morbid events, and size of the population studied. These criteria are met by the study of Greene and associates in short-term and medium-term follow-up. They report that using the Hopkins patient selection criteria, donor resources, and immunosuppressive regimens, a low (3.5%) 30-day mortality and an equally impressive 4-year survival rate of 79% were achieved. The hazards of rejection and infection decreased to a low but seemingly constant late rate, indicating the need for long-term surveillance.

Comparison between the morbidity and mortality data of Greene and associates and the reported experience of others is complicated, however, by several confounding considerations. First, meaningful comparison of rejection and infection frequency between reports requires precise, understandable, and widely recognized definitions of these morbid events. Consensus on such definitions often does not exist. For example, whereas most centers' diagnosis of rejection episodes requires biopsy histological confirmation showing a cellular infiltrate with myocyte necrosis, some groups treat rejection in the absence of myocyte necrosis. Second, infection and rejection may manifest in forms of varying severity and prognostic importance. Herpes zoster cutaneous eruption is not of equal clinical significance to herpes encephalitis even though positive cultures in the latter entity might not be obtainable. Rejection episodes with impressive cellular infiltrates on biopsy are most often asymptomatic and easily reversible, whereas rare humoral rejection episodes may result in severe hemodynamic compromise, frequently death, with minimal or even no cellular infiltrate present in endomyocardial biopsy specimens.

Third, morbidity and mortality have been shown to be adversely affected by such recipient selection criteria as the presence of congenital heart disease, female gender, and pulmonary hypertension. Use of mechanical assist devices preoperatively, particularly the Jarvik-7 artificial heart, may adversely affect transplantation outcome. Long duration of recipient waiting time for a donor heart may be deleterious to results of the procedure. Donor factors such as ischemic time, donor age, preservation technique, histocompatibility matching, ABO blood group matching, and dependence on inotropic support might be important influences on transplantation outcome.

The relative benefits of various immunosuppression regimens regarding morbidity and mortality remain to be defined. Though many reports attribute good transplantation outcome to a favored immunosuppressive protocol, perhaps different immunosuppressive protocols are better suited to individual recipient groups than others. For example, older recipients and newborns may require less intense immunosuppression than middle-aged patients, infants, and adolescents.

Despite the above considerations, the Hopkins report represents an impressive achievement that illustrates the remarkable progress that has been realized in heart transplantation in this decade. Heart transplantation has a profound impact on the prognosis of patients fortunate enough to receive a donor heart.

Tragically, only 2,000 of the 14,000 patients per year who would benefit from a cardiac allograft receive a transplant in the United States. Relaxation of selection criteria would perhaps quadruple the number of potential transplant recipients. The gap between present organ donor supply and demand is daunting and will almost certainly never be met by efforts to increase the supply of human donor organs. The donor shortfall should be a strong stimulus for further research in cross-species transplantation and mechanical cardiac replacement.

Many will argue that xenotransplantation and long-term mechanical cardiac replacement are unachievable goals; undoubtedly, a decade ago critics of like mind would have rejected the suggestion that the results reported by Greene and associates in this issue would ever be possible.

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A Quality Assurance Model of Operative Mortality in Coronary Artery Surgery

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Quality assurance in coronary artery bypass grafting (CABG) surgery requires a comparison of operative mortality against an accepted standard of care. Raw mortality statistics are unacceptable in this context, and risk factor analysis is essential. However, this principle has not been adequately demonstrated in previous reports. Our goal in this study was to develop a risk model of accepted CABG mortality and illustrate its proper use in coronary artery surgery. The model was derived from a Bayesian analysis of 6,630 patients undergoing CABG in the Coronary Artery Surgery Study (CASS) registry. Age, sex, ventricular function, previous myocardial infarction, extent of coronary artery disease, unstable angina, and surgical priority were used by the model to sort patients into risk categories. From January 1984 through December 1987, 840 patients underwent isolated CABG at our hospital. With raw mortality data, the 3.9% (33/840) mortality of our patients was significantly different from the 2.3% (153/6,630) CASS mortality ($p < 0.001$). When our patients were entered into the CASS model for risk stratification, however, our CABG mortality conformed to the CASS experience. These results illustrate the fallacy of using raw mortality statistics for interinstitutional comparisons. This type of risk model is a fundamental element of CABG quality assurance.

(Ann Thorac Surg 1989;47:646–9)

An effective quality assurance program compares operative results against accepted standards of care. However, it is quite difficult to apply this principle to the field of coronary artery surgery [1–4]. The major obstacle has been the need to account for all important risk factors so that patients can be sorted into appropriate risk categories [1, 3–5]. Certainly the use of raw statistical data without allowing for risk stratification is a disservice to patient and physician alike [4–6]. It should be possible to use a model of accepted operative mortality to compare the predicted results of the model against the observed results of patients in similar risk categories.

We have investigated this approach by developing a Bayesian model of the Coronary Artery Surgery Study (CASS) experience for comparison against our own operative experience. The model has been derived with particular attention to ensure that patients are closely matched and stratified according to preoperative risk factors.

Risk stratification is an essential element of quality assurance [1, 2, 4–7]. The CASS group developed a logistic risk equation [8] to address this issue, but its cumbersome nature has precluded practical application [1]. More recently, we [4] have used a Bayesian algorithm to sort patients into major risk categories. Our success in using this method to model our own operative experience encouraged us to use a similar system to represent the CASS results. The technique is completely general and can be applied to other clinical areas.

Material and Methods

The Bayesian model was developed according to previously published guidelines [4, 9], and was designed to predict the probability of death after coronary artery bypass grafting (CABG) based on the reported experience of the CASS registry. There are several studies detailing the composition of CASS registry patients, but the most complete for the purpose of this study was that of Kennedy and colleagues [10] from the Coordinating Center for Collaborative Studies in Coronary Artery Surgery.

Two prognostic categories were considered: survival and death. Seven preoperative patient variables generally regarded as important risk factors were selected: age, sex, ejection fraction, extent of coronary artery disease, previous myocardial infarction, unstable angina, and surgical priority. These risk factors were used to determine the conditional probabilities associated with each prognostic category (Table 1). The resultant conditional probability matrix was then incorporated into a computerized Bayesian algorithm to serve as a model of CASS operative mortality. For any given patient, the model analyzes these seven risk factors to generate a prediction of the probability of operative death for that patient based on the reported CASS experience.

The patient population for entry into this model was drawn from the recent operative experience at Walter

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Table 1. Conditional Probabilities From CASS Registry[a,b]

Variable	Survivors (n = 6,477)	Deaths (n = 153)
Age (yr)		
<50	1,738 (27)	22 (14)
50–70	4,530 (70)	113 (74)
>70	209 (3)	18 (12)
Sex		
Male	5,464 (84)	105 (69)
Female	1,013 (16)	48 (31)
Ejection fraction (%)		
>50	3,839 (78)	74 (70)
30–50	977 (20)	27 (25)
<30	102 (2)	5 (5)
Coronary artery involvement		
Left main	976 (15)	37 (24)
3 Vessels	3,198 (50)	92 (61)
2 Vessels	2,018 (31)	43 (28)
1 Vessel	1,196 (19)	17 (11)
Previous myocardial infarction	3,413 (53)	84 (55)
Unstable angina	2,652 (41)	96 (63)
Surgical priority		
Routine	5,129 (80)	89 (59)
Urgent	1,062 (17)	39 (26)
Emergent	189 (3)	23 (15)

[a] The number of patients in each prognostic category (survivors or deaths) that have the designated risk factor. The percentage of patients is shown in parentheses. For example, of those who survived, 1,738 or 27% (1,738/6,477) were less than 50 years old. [b] Ejection fraction calculations were based on a total of 5,024 patients, coronary artery involvement was based on 6,564 patients, and surgical priority was based on 6,531 patients as reported by Kennedy and colleagues [10]. The other calculations were based on 6,630 patients.

Table 2. Characteristics of the 840 Patients[a]

Variable	Survivors (n = 807)	Deaths (n = 33)
Age (yr)		
<50	180 (22)	3 (9)
50–70	551 (68)	23 (70)
>70	76 (9)	7 (21)
Sex		
Male	693 (86)	24 (73)
Female	114 (14)	9 (27)
Ejection fraction (%)		
<30	34 (4)	4 (12)
30–50	168 (21)	12 (36)
>50	605 (75)	17 (52)
Coronary artery involvement		
Left main	127 (16)	8 (24)
3 Vessels	549 (68)	26 (79)
2 Vessels	186 (23)	7 (21)
1 Vessel	72 (9)	0
Previous myocardial infarction	353 (44)	15 (45)
Unstable angina	109 (14)	13 (39)
Surgical priority		
Elective	517 (64)	14 (42)
Urgent	201 (25)	10 (30)
Emergency	89 (11)	9 (27)

[a] Numbers in parentheses are percentages.

Reed Army Medical Center. From January 1984 to January 1988, 895 consecutive patients underwent isolated CABG at our hospital. Insufficient clinical information eliminated 38 of them (none of whom died) from the study. Seventeen patients were taken to the operating room with an evolving myocardial infarction and severe hemodynamic compromise, thereby making them inappropriate for comparison with CASS patients. The remaining 840 patients made up the population evaluated by the CASS model (Table 2).

Surgical priority was assigned using definitions similar to those used by the CASS group [4, 8, 10]. Emergency operations were usually performed within one hour of catheterization or clinical deterioration. Procedures were classified as urgent if CABG was necessary within two days of catheterization. All others were considered elective.

Operations were performed using cardiopulmonary bypass and moderate systemic hypothermia with topical cooling. Cold potassium crystalloid or blood cardioplegia was used in all patients. Venting was usually established by way of the ascending aorta, but this depended on the preference of the operating surgeon. Distal coronary anastomoses were performed first, and the proximal anastomoses were performed over a partial occlusion clamp during the rewarming phase.

The presence or absence of the seven risk factors was noted for each of the 840 patients. Individual patient data were then entered into the CASS model, and a prediction of the probability of operative death was obtained for each patient. This allowed the patients to be grouped into risk categories, as shown in Table 3. The observed mortality for each category was obtained by tabulating the actual number of deaths that occurred in that group. A compar-

Table 3. Predicted Versus Observed Operative Mortality

Predicted Mortality (%)	Observed Mortality[a] (%)	95% Confidence Limits[b]
<5	2.7 (17/625)	1.6%–4.4%
5–25	3.5 (5/139)	1.3%–8.6%
25–50	13.7 (7/51)	6.1%–26.8%
>50	16.0 (4/25)	5.2%–36.9%
>75	40.0 (2/5)	7.3%–82.9%

[a] Within the parentheses, the numerator is the number of deaths and the denominator is the total number of patients in that risk category. [b] The confidence limits indicate that one can be 95% certain that the "true" observed mortality will lie within the specified interval.

ison of the predicted and observed mortality is also shown in Table 3.

Results

In our population, 33 deaths occurred at some point during the hospitalization for CABG. The overall mortality for the group of 840 patients was 3.9% (33/840). Urgent or emergent operations made up 37% (309/840) of this series and accounted for 58% (19/33) of the deaths. Forty-three of the 840 patients were undergoing reoperative CABG. Additional clinical details of the patient population are given in Table 2.

Using only raw mortality data, a χ^2 analysis showed that the CASS mortality of 2.3% (153/6,630) is significantly less than the 3.9% mortality of our series ($p < 0.001$). When our patients are stratified according to risk, however, the operative mortality in our series is actually less than what would be anticipated from the CASS experience. As an example, 25 patients were predicted to have an operative mortality of more than 50% (see Table 3). Based on the CASS experience, at least 13 of these patients would have been expected to die after CABG. In fact, only 4 of them—or 16%—died, indicating that our results were in keeping with the standards of the CASS group. The same can be said for each of the remaining risk categories.

Comment

These results illustrate the fallacy of using raw mortality data to analyze operative results. A valid comparison must account for risk factors that permit stratification into patient subgroups that are at different levels of risk for CABG procedures [2, 3, 5, 7, 8]. Once patients have been sorted into such risk categories, then reasonable interinstitutional comparisons can be made.

It is clearly desirable to use a model that analyzes individual patient risk factors to generate an estimate of the probability of operative death for the given patient. The model should be able to account for a large number of risk factors and should be sufficiently flexible to undergo changes in its data base as changes in the patient population occur with time. Both logistic risk equations [8] and the theorem of Bayes [4] satisfy these requirements. Logistic equations, however, have been somewhat difficult to apply on a practical basis [1, 4]. We believe that Bayesian algorithms offer more flexibility in this clinical context, and have chosen to develop our model using previously described Bayesian techniques [4, 9]. Certainly logistic regression models would be acceptable as well.

Regardless of the mathematical algorithm, one must select appropriate risk factors for consideration. There is an enormous body of information suggesting the most important risk factors for CABG, but conclusions vary from one report to another [1–4, 7, 8, 10–14]. We have chosen those patient parameters that are generally regarded as significant predictors of operative mortality [5, 7, 10, 12, 13]. As we [4, 9] have stated in earlier studies, we believe that a problem of this complexity requires the analysis of a large number of parameters. Certainly reoperation should ideally be included among the list of important risk factors. However, it is not possible to obtain all the information we would like from published CASS reports.

In deciding to use CASS for our data base, we were confronted with the choice of using all available data from one report or perhaps gathering more data from reports published at different times. However, because it is necessary to base the Bayesian conditional probabilities on a single patient population, we relied on a single report [10]. The use of information gathered from reports that span several years may introduce temporal variables that would adversely affect the validity of the model.

Our choice of CASS to represent a standard of care was completely arbitrary. There are a number of reasonable objections to this choice. Generally the CASS population is made up of patients falling into the lower end of the CABG risk spectrum [3, 12, 14]. In addition, many of these CASS patients underwent CABG a decade ago and therefore may not represent a true reflection of current risks. We recognize that other objections to the CASS registry can be raised [11–13], but we believe that CASS is a reasonable choice in this clinical context. We would not contend that CASS results are the best possible, but they do reflect at least an acceptable average standard of care [8, 11]. As mentioned, the approach we have used is completely general, and others may choose an alternative to represent the standard.

The major shortcoming of this study is that the CASS model has not been tested against CASS registry patients to confirm its validity. Statistical theory dictates that the Bayesian model will provide an accurate portrayal of the CASS experience, but without direct access to that registry, that cannot be verified. Perhaps such information from this government-funded study can be made available in the future so that the development of operative risk models can be facilitated.

It should be emphasized that no attempt has been made here to identify the most important risk factors. That is the task of variate analysis, which has been described in great detail in numerous other publications. The purpose of the Bayesian algorithm is to use preoperative patient risk factors to generate a prediction of the probability of operative death for a single given patient. Although it may be important to recognize the most important risk factors derived from large patient surveys, that information has little relevance to the single patient who is seen with a myriad of clinical characteristics that are not specifically addressed in these large trials. One must be able to predict the risk to that individual patient.

The algorithm presented here allows the surgeon to do exactly that. One enters the preoperative risk factors of the patient into the computer program, and the program uses a Bayesian formula to estimate the probability of operative death based on the data base of previous clinical experience.

In recent years, CABG operative mortality has come under close investigation. As responsible surgeons we welcome that scrutiny, but we must insist that standards of comparison fully account for the preoperative risk factors associated with CABG. The use in 1986 of raw mortality statistics by the Department of Health and Human Services Health Care Financing Administration illustrates the misconceptions that can arise from inappropriate application of unsorted patient data [5, 15]. The Society of Thoracic Surgeons [5] has responded with a statement of concern expressing serious reservations about the use of Health Care Financing Administration data to suggest a "quality of care" standard. If we condemn this simplistic application of mortality data, though, we are obligated to propose a more acceptable alternative. The statement of concern emphasizes that risk factors predictive of operative mortality must be identified and subjected to appropriate statistical analysis before comparisons of mortality rates between institutions can be made. It further encourages the development of statistical models to sort patients into risk categories.

In this study, we have presented such a model of operative risk. Although this model may not be ideal, it does provide an improved instrument of quality assurance that is based on sound principles of surgical risk assessment. Techniques of this kind may encourage other institutions to critically review their operative results by making valid comparisons against a selected standard.

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Exploratory Analysis of Time-Dependent Risk for Infection, Rejection, and Death After Cardiac Transplantation

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Data from 95 heart transplantations performed at The Johns Hopkins Hospital from July 1983 to October 1988 were analyzed to detect patterns of morbidity and mortality. Using nonparametric techniques, hazard functions were determined for all deaths and for deaths due to infection or rejection. The rates of rejection and infection (episodes per patient-month) were determined within each of ten intervals following transplantation. A total of 19 deaths, 281 rejection episodes, and 180 distinct infections were available for analysis during a follow-up of 1 to 62 months. The hazard function for rejection appeared biphasic, with a rapidly decelerating early phase during the first year followed by a constant late phase. The hazard function for infection was triphasic, with a delayed, decelerating early phase, a period of increased risk approximately 2 years after operation, and finally a late constant phase. Both infection and rejection rates (episodes per patient-month) were biphasic, with rapidly decelerating early phases and constant late phases. Multiple regression analysis demonstrated that eventually nonsurviving patients had significantly higher rates of rejection and infection during both the early and late phases compared with survivors. The increased rate of rejection among nonsurvivors was evident throughout follow-up, although no deaths were attributable directly to rejection after the first 8 months. These data suggest that a complex interrelationship between infection and rejection determines late survival after cardiac transplantation and that aggressive treatment of late rejection predisposes toward death from infection.

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Refinements in the management of cardiac transplant recipients have improved 1-year survival from 67% in 1979 to greater than 90% in 1988, thereby making cardiac transplantation accepted therapy rather than an experimental procedure. Advances in immunosuppression and management of immunosuppressed patients probably account for most of the improvement in survival, which has occurred despite extended application of cardiac transplantation to younger, older, and sicker patients [1–3]. An understanding of risk factors for death and morbidity after transplantation is crucial to further advances.

Even in the cyclosporine era, rejection and infection remain the greatest threat to the survival of heart recipients [4–7]; together they account for the majority of deaths. Although therapeutic immunosuppression is vital to long-term graft function and survival, all immunosuppressive regimens compromise the patient's immune defenses, resulting in increased susceptibility to rare opportunistic organisms as well as common bacterial and viral pathogens. Thus, there is an obligate interdependence between rejection and infection in the organ transplant recipient. The present analysis of our heart transplant experience was undertaken to better understand the complex relationships among morbid and mortal events due to rejection and infection in heart transplant recipients.

Material and Methods

Study Population

Initial experience with our heart transplant program has been described elsewhere in detail [8, 9]. Briefly, between July 1983 and October 1988, 95 patients underwent isolated cardiac transplantation at The Johns Hopkins Hospital. The number of patients undergoing the procedure each year over the study period is shown in Table 1. Primary diagnoses in the recipients were coronary artery disease (n = 28, 30%), cardiomyopathy (n = 60, 63%), myocarditis (n = 3, 3%), and congenital heart disease (n = 4, 4%). Seventy-seven (81%) of the recipients were male and 18 (19%) were female. Mean age was 41 years (range, 0.7 to 62 years).

Of the donors, 74 (78%) were male and 21 (22%) were female; mean donor age was 25 years (range, 0.5 to 47 years). Heart procurement was distant in 86 instances (91%) and local in nine (10%), with a mean ischemic time of 174 minutes (range, 75 to 320 minutes). Fifty-five donors (58%) died of head trauma, 16 (17%) died of gunshot wounds, 17 (18%) died of cerebrovascular events, and the remaining died of a variety of other causes.

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Table 1. Heart Transplantations Performed at The Johns Hopkins Hospital, July 1983 Through September 1988

Year	Heart Transplantations
1983	4
1984	13
1985	21
1986	28
1987	20
1988	9
Total	95

Immunosuppression

Our current immunosuppression protocol is outlined in Table 2. Preoperatively, cyclosporine was administered orally at a dose of 10 mg/kg; if the patient's serum creatinine level was greater than 2 mg/dL, the dose was reduced to 6 mg/kg. Cyclosporine was given postoperatively at doses to provide a whole blood level of 100 to 200 ng/mL by high-performance liquid chromatography. Methylprednisolone sodium succinate was given intravenously intraoperatively; prednisone and azathioprine were begun when oral intake resumed. Patients were discharged from the hospital on a regimen of prednisone, 30 mg daily (approximately 0.4 mg/kg), and the dose was tapered over several months to 0.2 mg/kg.

Azathioprine administration was started in the postoperative period at 2 mg/kg and adjusted to suppress the peripheral white blood cell count to approximately 5,000/mL. Prophylactic antithymocyte globulin was not used in any patient.

Rejection

Surveillance for rejection was performed by endomyocardial biopsy every seven to ten days for the first 6 postoperative weeks and at monthly intervals for the next 90 days. Thereafter, frequency of biopsy was reduced to every 3 months or more often if clinically indicated.

Rejection was diagnosed by biopsy according to the histological criteria of Billingham [10]. An interstitial infiltrate indicated mild rejection, and an increased infiltrate with myocyte necrosis defined moderate rejection. Immunosuppression was modified only in patients with moderate or severe rejection; only these treated episodes were tabulated in our analyses of rejection episodes. A rejection episode was not judged resolved until endomyocardial biopsy specimens indicated absent or mild rejection; thus, several consecutive positive biopsy specimens were considered only a single episode of rejection.

Rejection was generally treated with oral administration of prednisone (100 mg daily for three days) followed by a tapering of the dose over 2 weeks to 5 mg daily. If no improvement in biopsy results was observed, methylprednisolone (1 g/day) was given intravenously for three days, followed by a prednisone taper. Refractory rejection episodes were treated with equine antithymocyte globulin (ATGAM) or murine monoclonal antibodies (OKT3).

Infection

Infections were considered clinically important only if microbial cultures were positive and the patient required intravenous therapy for the illness. Multiple consecutive positive microbial cultures from the same body site were considered part of the same infectious episode. Clinically important infections at different sites were considered separate infectious episodes even if they involved the same organism.

Statistical Analysis

Data were collected prospectively in an ongoing transplant patient data base and were analyzed using BMDP Statistical Software [11]. The cumulative survival function was estimated by the actuarial (life-table) method and its approximate standard error determined by the Greenwood formula [11] for each of ten intervals following transplantation. The hazard function, or instantaneous death rate, was estimated nonparametrically at the midpoint of each life-table interval [11]. This method gives a "piecewise-constant" estimate of the hazard function [12]; for smooth graphic display, the estimates from adjacent intervals were connected by cubic spline interpolation.

Rejection and infection episode rates were calculated as the number of events (as already defined) occurring per patient-month during each interval. By analogy to the actuarial (life-table) method of estimating number of patients at risk during each interval, those who died or were censored (ie, were not followed for the entire interval) were considered to be at risk for one half of the interval. Implicit in this calculation is the assumption that risks of the events studied (rejection and infection, death or censorship) were constant within each interval.

Infection and rejection episode rates were determined separately for patients currently alive (survivors) and those dead (nonsurvivors) by the method described (number of episodes per patient-month at risk). To test for

Table 2. Immunosuppression Protocol

Time	Solu-Medrol	Prednisone	Azathioprine	Cyclosporine
Preop	. . .	. . .	. . .	10 mg/kg
Intraop	500 mg/kg	. . .	. . .	. . .
Postop	125 mg q 8 h × 3 doses	1 mg/kg tapered to 0.4 mg/kg	2 mg/kg	10 mg/kg
Long term	. . .	0.2 mg/kg	1–3 mg/kg	5 mg/kg

Prednisone, azathioprine, and cyclosporine doses are total daily doses.

Solu-Medrol = methylprednisolone sodium succinate.

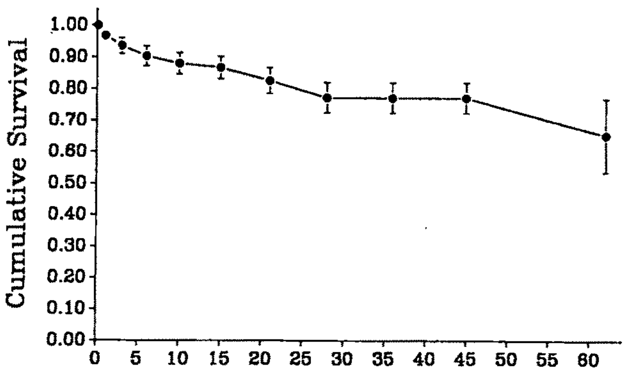

Fig 1. Cumulative survival for 95 patients undergoing cardiac transplantation. Error bars represent the standard error of the mean.

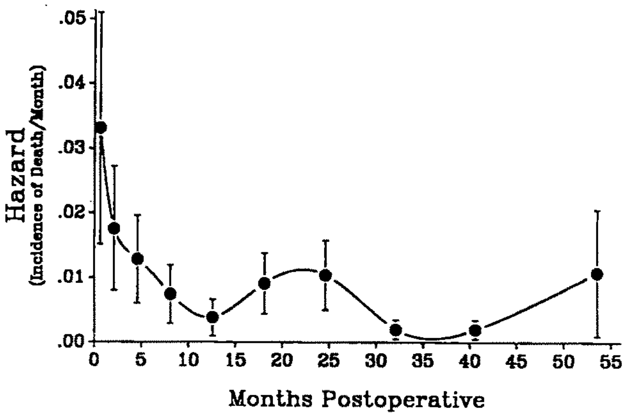

Fig 2. Total hazard for death after cardiac transplantation. Error bars represent the standard error of the mean.

trends and group differences in these rates, survivors and nonsurvivors were compared during early and late postoperative phases using multiple linear regression weighted by sample size [13]. The two predictor variables considered for each analysis were number of postoperative months and survivor versus nonsurvivor status.

Results

Figure 1 contains the actuarial survival curve for the 95 patients in this series undergoing cardiac transplantation. Actuarial survival was 88% at 12 months and 79% at 48 months. The causes of death are displayed in Table 3. Four patients died of acute rejection and 10, of infection. Two died of carcinoma or lymphoma and 2, of pulmonary hemorrhage. One patient died of myocardial infarction. Four of these patients died during the initial hospitalization: 2 had pulmonary hypertension with right ventricular failure, and 2 had sepsis with multiple-organ failure.

The nonparametric estimate of the hazard function for death from all causes is shown in Figure 2. Although the standard errors are large, there is a triphasic pattern: first, an early phase of rapidly decelerating risk lasting most of the first postoperative year; second, an intermediate phase of resurgent risk peaking at the end of the second year; and third, a late phase of low but increasing risk beginning at the end of the third year. Estimates of the shape of the hazard curve during this late phase are limited by the small number of patients followed this long and the high ratio of censor rate to death rate [12]. The late rise in hazard is due to a single death among 6 patients at risk at the start of the last interval.

Table 3. Causes of Death of 19 Nonsurvivors of Cardiac Transplantation[a]

Cause	No. of Patients
Infection	10 (52)
Rejection	4 (21)
Pulmonary hemorrhage	2 (11)
Neoplasm	2 (11)
Myocardial infarction	1 (5)

[a] Numbers in parentheses are percentages of all deaths.

Separate hazard functions describing instantaneous risk of death from infection and risk of death from rejection are contained in Figure 3. Whereas both rejection and infection hazards are high in the immediate postoperative period, the rejection death hazard decreases to a low, constant level after the first 10 months. However, the hazard for death from infection increases during the second postoperative year before returning to a low late phase that is similar to the rejection hazard. Thus, the increase in total hazard or risk of death from any cause during the second postoperative year is explained for the most part by an increase in risk of death from infection.

Figure 4 shows the rejection and infection episode rates calculated during each of the ten postoperative intervals. Although early rejection rates are higher than infection rates, the curves have a common pattern of a rapidly declining early phase during the first postoperative year followed by a low, constant late phase. Thus, the increased hazard observed at the end of the second postoperative year (see Fig 3) is not explained by a corresponding

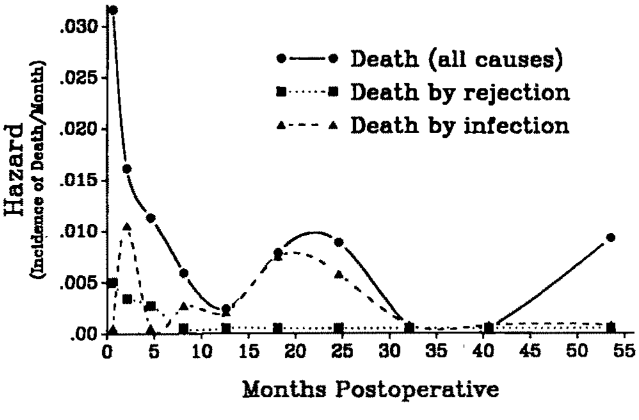

Fig 3. Hazard functions for death from all causes, death from rejection, and death from infection after cardiac transplantation.

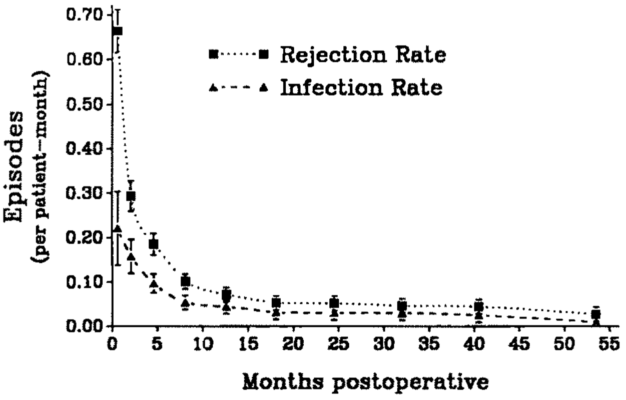

Fig 4. Rates of rejection and infection after cardiac transplantation. Error bars represent the standard error of the mean.

Table 4. Results of Multivariate Analysis of Rejection and Infection Rates

Event	Phase	Multiple R^2	Variable[a]	p Value
Rejection	Early	0.89	Time	0.103
			Group	0.001
	Late	0.94	Time	0.014
			Group	0.001
Infection	Early	0.88	Time	0.103
			Group	0.007
	Late	0.72	Time	0.135
			Group	0.026

[a] Time variable is months after transplantation (midpoint of interval). Group variable is present survivors or eventual nonsurvivors.

increase in rejection or infection episode rates during this period.

When rejection and infection rates of survivors and nonsurvivors were compared, a different pattern emerged. The rejection episode rates for nonsurvivors were greater than those of survivors (Fig 5). This difference between groups was confirmed by separate multiple regression analyses for the early and late postoperative phases (Table 4). Notably, although rejection was not the major cause of death for any patient after the eighth postoperative month, nonsurvivors had higher rejection rates than survivors throughout the entire study period.

Figure 6 shows a similar comparison of infection rates between survivors and nonsurvivors. The two groups were significantly different by multiple regression analysis (see Table 4). A high infection rate was observed among nonsurvivors in the second postoperative year, as predicted by the increase in hazard for fatal infection during the same period.

Comment

Early experience in cardiac transplantation at Stanford showed that acute rejection occurred more frequently in the first 3 postoperative months than in subsequent months [1]. Similarly, infection rates decreased significantly in the first year after operation. Mortality after transplantation also followed a similar pattern, high early risk followed by late low risk.

The decline in risk of these events—rejection, infection, and death—has usually been described in terms of linearized rate, ie, episodes per patient-month of follow-up. Most studies have arbitrarily divided the postoperative period into early (first 3 postoperative months) and late (beyond the third postoperative month) phases. These linearized rates ignore the continuous nature of risk functions and obscure variations of episode rates within the interval period.

We chose to examine our transplantation experience with nonparametric techniques that recognize the continuous and time-dependent nature of these episode rates. These techniques offer several advantages over simple linearized rate estimates. First, they do not assume that rates and hazards are constant over long periods. Second, they permit better resolution of time-dependent events and their rates within the conventional early and late phases. Third, they allow fairer comparisons of rates and hazards between treatment groups and institutions, especially if follow-up periods are not equal.

The use of the hazard function (instantaneous risk of

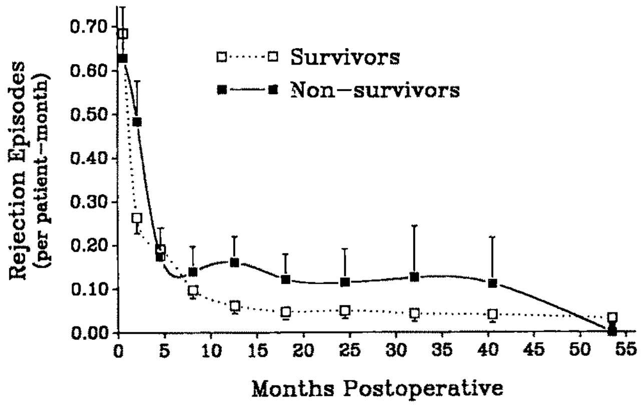

Fig 5. Rates of rejection among eventual survivors and nonsurvivors of cardiac transplantation. Error bars represent the standard error of the mean.

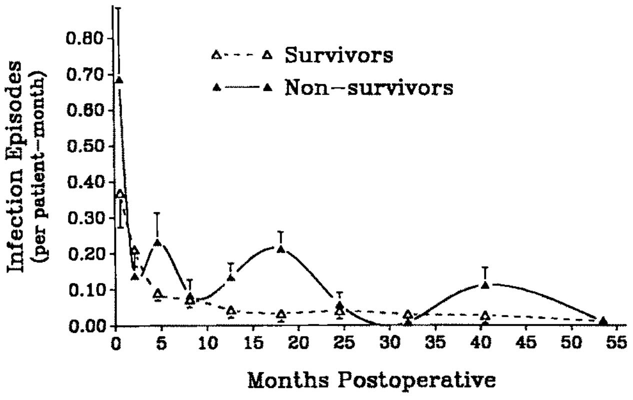

Fig 6. Rates of infection among eventual survivors and nonsurvivors of cardiac transplantation. Error bars represent the standard error of the mean.

death) to analyze results of surgical procedures has been popularized by Kirklin and associates at the University of Alabama [14]. Their analysis of morbid events and risk factors for death after cardiac transplantation suggested a biphasic hazard function: a high risk of death immediately after operation followed by a decline to a low, constant risk after the first 3 months [15]. The time-varying hazard is separated into phases [16] by mathematically complex parametric methods. We have chosen a nonparametric approach. Although more likely to reflect spurious patterns within the data set [17], this technique can, nonetheless, provide clinically important information on the pattern of morbidity and mortality.

Our estimates of the risk of rejection and infection still have limitations. In the case of rejection, frequency of surveillance by endomyocardial biopsy decreases during follow-up; in itself this might lead to lower observed rejection rates during the late period if rejection is a low-probability event. A different sampling rate might also explain part of the observed discrepancy in rejection and infection rates in survivors compared with nonsurvivors, as the latter group may be hospitalized more often and subjected to greater scrutiny. Nevertheless, it seems unlikely that sampling rates account for all observed differences.

In our series, the hazard for death after cardiac transplantation appears multiphasic. The increased risk of death near the end of the second postoperative year results mainly from an accelerated risk of fatal infection, as no deaths were attributable directly to rejection after the first 8 months. Although the late risk of rejection was low in the series, patients who subsequently died had higher rates of rejection than those surviving. These nonsurviving patients may be dying of infection as a consequence of augmented immunosuppression for their higher rejection rates. Less aggressive treatment of late episodes of rejection might reduce the mortality associated with infection. Although this strategy might increase the risk of death by rejection, this effect may be more than offset by a reduction in risk of death from infection, with improvement in overall survival.

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A Comparison of Mitral Valve Reconstruction With Mitral Valve Replacement: Intermediate-Term Results

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The continued good results after mitral valve reconstruction prompted this retrospective study to compare operative and late results from our institutional experience since 1976 with 975 porcine mitral valve replacements (MVRs) (1976 to December 1987), 169 mechanical MVRs (1976 to December 1987), and 280 Carpentier-type mitral valve reconstructions (CVRs) (1980 to mid-1988). The operative mortality was 2.0% for isolated CVR, 6.6% for isolated mechanical MVR, and 8.5% for isolated porcine MVR. The overall operative mortality was 5.0% for CVR, 16.6% for mechanical MVR, and 10.6% for porcine MVR. The overall 5-year survival including hospital deaths was 76% for CVR, 72% for mechanical MVR, and 69% for porcine MVR. By multivariate analysis, the predictors of increased operative risk and of decreased survival were age, New York Heart Association functional class IV status, previous cardiac operation, and performance of concomitant cardiac surgical procedures. The type of valvular procedure was not predictive of operative risk or overall survival. The 5-year freedom from reoperation was 94.4% for nonrheumatic patients having CVR, 77.4% for rheumatic patients having CVR, 96.4% for mechanical MVR, and 96.6% for porcine MVR ($p < 0.05$, rheumatic patients with CVR versus both MVR groups). The 5-year freedom from all valve-related morbidity and mortality was significantly better for valve reconstruction compared with both types of valve replacement. Thus, the operative risk and late survival obtained after mitral valve reconstruction were at least equivalent to those obtained after MVR. In addition, patients receiving mitral valve reconstruction had less valve-related combined morbidity than patients receiving valve replacement, thus making mitral valve reconstruction preferable in some patients with mitral insufficiency.

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Although mitral valve annuloplasty techniques were used successfully in select patients as early as 1957 [1, 2], mitral valve replacement (MVR) became a much more widely used procedure as a result of its predictable efficacy. However, both mechanical and porcine prosthetic mitral valves continue to have certain limitations, primarily related to thromboembolism and anticoagulant-related hemorrhage [3]. In addition, porcine prosthetic valves have shown a substantial risk of late valve degeneration between 7 and 15 years postoperatively.

Encouraged by the work of Carpentier and his group [4, 5] and others [6–9], we developed a renewed interest in mitral valve reconstruction during the past decade. This report retrospectively analyzes the New York University experience with mitral valve repair and replacement since 1976 by comparing the late results after Carpentier-type mitral valve reconstruction with those obtained after porcine or mechanical MVR.

Material and Methods

Basic Characteristics of the Study Group

Most of the operative procedures performed on the mitral valve, except classic open mitral commissurotomy, between 1976 and 1987 at our institution were included in this report. The patient study group was divided into three major categories: 975 porcine valve replacements (1976 to December 1987), 169 mechanical valve replacements (1976 to December 1987), and 280 Carpentier-type mitral valve reconstructions (CVRs) (1980 to mid-1988).

Age at operation was different for the three groups (mean age of the porcine valve replacement group, 60.7 years, range, 6 to 88 years; mean age of the mechanical valve replacement group, 57.6 years, range, 11 to 83 years; mean age of the CVR group, 54.5 years, range, 3 to 83 years; $p < 0.05$ for all differences). The CVR group had a higher prevalence of male patients (50%) than either the mechanical MVR (34%) or the porcine MVR group (38%) ($p < 0.001$). Previous cardiac surgical procedures had been performed in 22% of the porcine MVR group and 47% of the mechanical MVR group, but in only 10% of the CVR group ($p < 0.001$). Previous mitral valve commissurotomy had been performed in 14% of the porcine MVR group, 19% of the mechanical MVR group, and 4% of the CVR

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Table 1. Preoperative Characteristics of Patient Groups

Variable	Repair (n = 280)	Porcine Replacement (n = 975)	Mechanical Replacement (n = 169)	p Value
Time interval	1/80–5/88	1/76–12/87	1/76–12/87	. . .
Age (yr)[a]	54.5 ± 17.7	60.7 ± 10.8	57.6 ± 11.9	<0.05
Sex (%)				
Female	49.6	62.2	65.7	<0.001
Male	50.4	37.8	34.3	
Preop NYHA class (%)				
III	56.2	47.7	30.9	<0.001
IV	21.2	46.0	64.8	
Previous cardiac operation (%)	9.6	21.7	47.3	<0.001

[a] Data are shown as the mean ± the standard deviation.

NYHA = New York Heart Association.

group ($p < 0.01$), and previous MVR had occurred in 6% of the porcine and 23% of the mechanical MVR groups ($p < 0.05$). Thus, the valve reconstruction group was significantly younger and had had significantly fewer previous cardiac surgical procedures (Table 1).

Operation was for pure mitral regurgitation in 35% of the porcine MVR group, 35% of the mechanical MVR group, and 76% of the CVR group and for combined mitral stenosis and mitral regurgitation in 36%, 34%, and 24%, respectively. Pure mitral stenosis was the pathophysiology in 29% of the porcine and 31% of the mechanical MVR groups. No patient in the CVR group had pure mitral stenosis, as patients receiving open mitral commissurotomy were excluded.

Preoperative New York Heart Association (NYHA) classification was also significantly different. The reconstruction group had more NYHA class I or II patients and fewer NYHA class III or IV patients than the other two groups ($p < 0.001$) (see Table 1).

Operative Technique

Both membrane and bubble oxygenators were utilized along with the DeBakey roller pump for extracorporeal circulation. Moderate systemic hypothermia (25° to 30°C) was employed with flow rates between 1.5 and 2.3 L/min/m^2. Cold blood potassium cardioplegia was used for myocardial protection, with reinjections every 20 to 30 minutes to maintain a myocardial temperature of lower than 15°C. This was supplemented with topical hypothermia by continuous irrigation of cold saline solution over the heart, which was wrapped in a cold laparotomy pad.

Overall, each reconstructive technique described by Carpentier and colleagues [4, 5] was used in the CVR group, with more than 95% of the patients receiving two or more reconstructive procedures on the mitral valve. The Carpentier ring was inserted in 84% of the patients. Our operative techniques and approach to mitral reconstruction have been previously described [10, 11].

In the porcine MVR group, 71% received Carpentier-Edward valves and 29%, Hancock valves. In the mechanical valve group, 38% received Starr-Edwards valves, 50% received Björk-Shiley valves, 9% received St. Jude valves, and 3% received other mechanical valves. All valves were inserted with a Teflon pledget–reinforced horizontal mattress suture technique.

Operative repair or replacement of another cardiac valve was performed concomitantly in 39% of the porcine MVR group, 43% of the mechanical MVR group, and 19% of the CVR group, and concomitant coronary artery bypass grafting was performed in 19%, 15%, and 23%, respectively. Taking into account all other concomitant operative procedures as well as patients who underwent more than one type of concomitant operative procedure, a large and roughly equivalent percentage of the patients in each mitral group underwent concomitant cardiac surgical procedures (55%, porcine valve group; 52%, mechanical valve group; 48%, CVR group; $p > 0.05$) (Table 2).

Follow-up Data

Follow-up information obtained by telephone interview or office examination was 96% complete for the porcine valve group, 99% complete for the mechanical valve group, and 100% complete for the CVR group. The mean follow-up was 38.7 ± 24.7 months (range, 1 to 104 months; total, 2,816 patient-years) for the porcine MVR group, 42.3 ± 38.0 months (range, 1 to 143 months; total, 507 patient-years) for the mechanical MVR group, and 22.5 ± 20.0 months (range, 1 to 93 months; total, 498 patient-years) for the CVR group. If the cause of any late death could not be clearly determined because it occurred suddenly, outside the hospital, or without an autopsy, the death was classified as cardiac related. Our methods for classifying valve-related morbidity and mortality conformed to the guidelines proposed by the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity [12].

Anticoagulation

All patients were placed on a regimen of crystalline warfarin sodium (Coumadin) on the third postoperative day and continued on this therapy for a minimum of 3 months postoperatively. The prothrombin time was maintained at 1.5 to 2 times the control level. For patients in the mitral reconstruction group, warfarin was often discontinued at the end of 3 months, and most were switched to antiplatelet therapy. Our general policy for valve reconstruction was that warfarin therapy should be continued on a long-term basis only if the patient sustained a

Table 2. Incidence of Concomitant Operative Procedures in Patient Groups

Procedure	Repair	Porcine Replacement	Mechanical Replacement	p Value
All types (%)	47.5	55.1	51.5	NS
CABG (%)	23.2	19.2	14.8	NS

CABG = coronary artery bypass grafting; NS = not significant.

thromboembolic event or was considered to be at especially high risk for late thromboembolic complications as a result of some well-known predisposing factor, such as a giant left atrium with atrial fibrillation or the presence of an associated valve prosthesis.

All patients in the mechanical MVR group were maintained on a long-term regimen of warfarin. The desired prothrombin time was 1.5 to 2 times the control level. The patients in the porcine MVR group were maintained on a regimen of warfarin therapy for the first 3 to 6 months postoperatively. Subsequently, they received anticoagulants selectively, with many being switched to antiplatelet therapy at that time.

Long-term care and anticoagulation therapy, however, were usually directed by the individual patient's primary physician. Of the CVR patients, 30% were receiving warfarin, 32% were receiving antiplatelet therapy only, and 38% were receiving no anticoagulation or antiplatelet therapy at the time of follow-up. Of the porcine valve group, 41% were taking warfarin, 25% were receiving antiplatelet therapy only, and 34% were receiving no anticoagulation or antiplatelet therapy at the time of follow-up. Of the mechanical valve group, 100% were receiving warfarin at the time of follow-up.

Data and Statistical Analysis

This study provided for the analysis of more than 150 specific data points for each patient. Preoperative and postoperative data were obtained by reviewing the patient's hospital record. Follow-up information was solicited directly from the patient at the time of follow-up office visit or by contacting the patient, the patient's physician, or both by telephone. All data were entered into a computer and analyzed by means of the statistical software package SPSS^x (SPSS Inc, Chicago, IL). Most analysis of the significance of difference in preoperative and postoperative characteristics was performed by χ^2 analysis or one-way analysis of variance as appropriate. The relative significance of multifactorial influences on an event was determined by multivariate regression analysis. Actuarial curves for mortality or late complications were obtained by the life-table method, and the significance of difference between groups was determined by means of the confidence interval test.

Table 3. Some Predictors of Differences in Operative Mortality for Patients Undergoing Repair or Replacement for Mitral Valve Dysfunction

Variable	*p* Value
Age	<0.001
NYHA class	<0.001
Previous cardiac operation	<0.02
Concomitant operative procedure	<0.004
Type of mitral valve operation	NS

NYHA = New York Heart Association; NS = not significant.

Results

Hospital Mortality

Operative mortality (30-day) was 2.0% for isolated CVR, 6.6% for isolated mechanical MVR, and 8.5% for isolated porcine MVR; overall operative mortality was 5.0% for CVR, 16.6% for mechanical MVR, and 10.6% for porcine MVR. When operative risk was analyzed by multivariate analysis, only age, NYHA functional class IV status, previous cardiac surgical procedures, and performance of concomitant cardiac surgical procedures proved to be correlated with increased operative risk (Table 3). The performance of mitral valve reconstruction instead of MVR was not in itself shown to be predictive of decreased operative risk.

Survival

Actuarial 5-year survival from all cardiac-related death was 81.0% for the CVR group, 73.9% for the mechanical MVR group, and 73.1% for the porcine MVR group ($p <$ 0.001, CVR versus mechanical or porcine MVR) (Fig 1). Actuarial 5-year survival from all deaths (operative or late, cardiac-related or noncardiac-related) was 76% for the

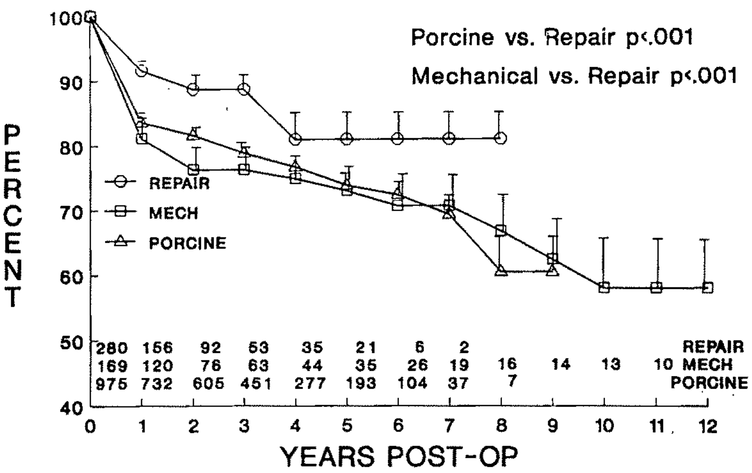
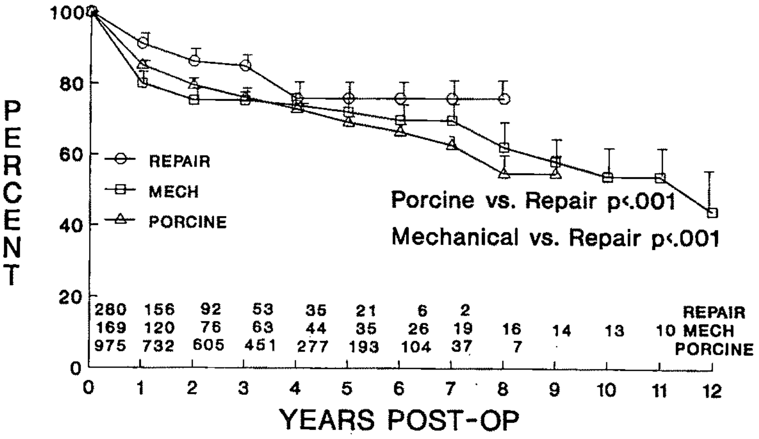


Fig 1. Actuarial survival from all cardiac-related death after mitral valve repair and mitral valve replacement.

Fig 2. Actuarial survival from all death after mitral valve repair and mitral valve replacement.



CVR group, 72% for the mechanical MVR group, and 69% for the porcine MVR group ($p < 0.001$, CVR versus mechanical or porcine MVR) (Fig 2). When overall survival was analyzed by multivariate analysis, age, NYHA class IV status, previous cardiac surgical procedures, and performance of concomitant cardiac surgical procedures were found to be predictive of late survival. By multivariate analysis, however, the performance of mitral valve reconstruction as opposed to MVR did not prove to be independently correlated with the 5-year survival rate.

Valve Durability and Freedom From Reoperation

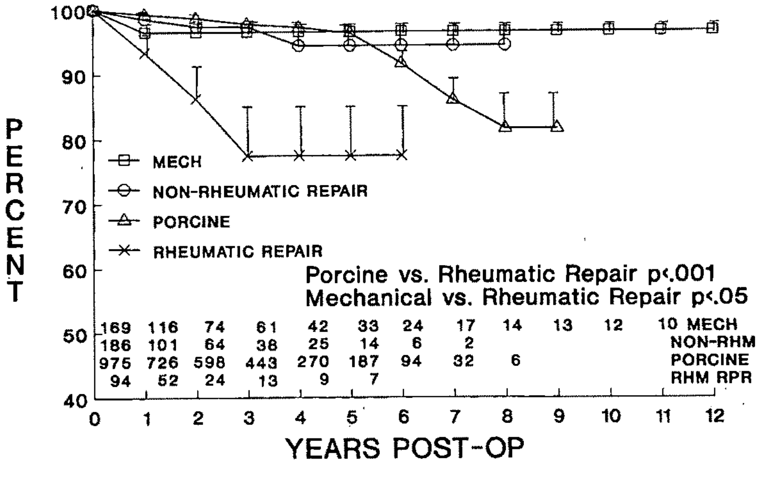
Because we [10] previously have found that both freedom from reoperation and functional valve durability after mitral valve reconstruction were dependent on the etiology of mitral insufficiency, we analyzed valve durability after mitral valve reconstruction separately for rheumatic and nonrheumatic groups. The actuarial 5-year freedom from all mitral valve reoperation was 94.4% for all nonrheumatic patients receiving CVR, 77.4% for rheumatic patients receiving CVR, 96.6% for patients having mechanical MVR, and 96.4% for patients having porcine MVR ($p < 0.05$, rheumatic CVR versus either MVR group) (Fig 3). Thus, nonrheumatic patients receiving mitral valve repair (n = 184) had a valve durability that was not significantly different from that noted in patients having valve replacement, whereas rheumatic patients receiving valve reconstruction (n = 96) had a significantly higher valve failure rate than patients undergoing valve replacement.

When the risk of valve failure was expressed in terms of hazard function, valve reconstruction patients demonstrated a high initial instantaneous risk of valve failure, followed by a very low constant late risk of valve failure (Fig 4). However, much of the early phase of increased risk is accounted for by valve failures in the rheumatic patients. The mechanical valve patients had a very low constant risk of valve failure after the first year. Notably, both the CVR and mechanical MVR patients showed a different pattern of interval risk for valve failure than was noted in the porcine MVR group (see Fig 4). Patients receiving porcine valves showed a relatively low risk of valve failure for early intervals, but demonstrated a rising hazard for valve failure when followed out to 104 months. This trend might continue to worsen if the study were carried out to 15 years.

Functional Improvement

Each group of patients showed excellent improvement in NYHA functional classification at follow-up, with 95.8% of the CVR, 90.2% of the mechanical MVR, and 75.9% of the porcine MVR patients improving to NYHA class I or II at follow-up ($p < 0.001$). Thus, although the functional status improved in all patients, patients undergoing valve

Fig 3. Actuarial freedom from any reoperation on the mitral valve after repair of nonrheumatic valves, repair of rheumatic mitral valves, porcine valve replacement of mitral valves, and mechanical valve replacement of mitral valves.



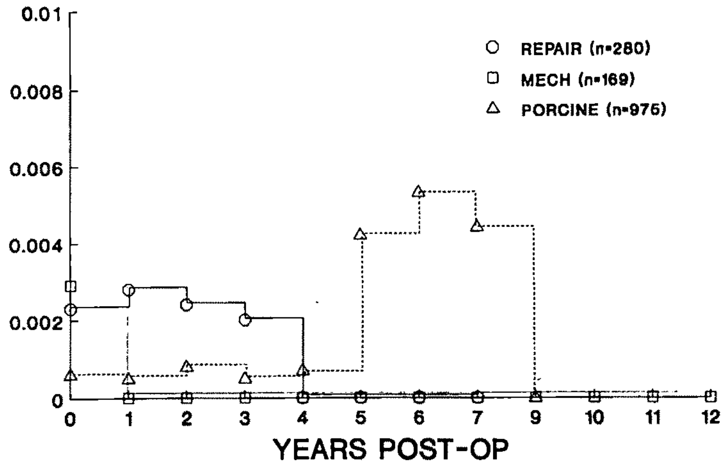


Fig 4. Interval hazard rate for all mitral valve reoperation after mitral valve repair and mitral valve replacement.

reconstruction were in a better functional class at the time of follow-up than patients undergoing valve replacement.

Thromboembolic and Anticoagulant-Related Complications

The 5-year freedom from thromboembolic complications was 94.1% after valve reconstruction, 94.0% after mechanical MVR, and 86.7% after porcine MVR ($p < 0.04$, porcine versus mechanical MVR) (Fig 5). However, because of the more extensive use of Coumadin in the valve replacement groups, the 5-year freedom from anticoagulant-related complications was 99.5% after valve reconstruction, but only 94.6% after mechanical MVR and 94.8% after porcine MVR ($p < 0.05$, CVR versus porcine MVR; $p = 0.06$, CVR versus mechanical).

Endocarditis

The 5-year freedom from late de novo endocarditis (excluding patients with ongoing intravenous drug addiction) was 100% after valve reconstruction, 95.7% after mechanical MVR, and 95.8% after porcine MVR ($p < 0.04$, CVR versus either MVR group) (Fig 6).

Overall Procedure-Related Morbidity and Mortality

If freedom from all valve-related morbidity and mortality (early and late) is analyzed, patients receiving valve reconstruction clearly have a higher freedom from valve-related morbidity and mortality events than patients receiving either type of replacement valve ($p < 0.002$, CVR versus either MVR group) (Fig 7). Also, the late-phase instantaneous risk of sustaining a valve-related complication or death is higher for both valve replacement groups compared with the valve reconstruction group (Fig 8). Thus, the actuarial combined risk of valve-related death or complication is significantly higher for patients having valve replacement than for patients having valve reconstruction.

Comment

These data clearly indicate that mitral valve reconstruction is not associated with an increased operative risk. In fact, several studies [13, 14] have suggested that the operative risk might actually be less than with valve replacement. However, these studies have not completely matched each group based on age, sex, and various risk factors.

The present study of most patients undergoing mitral valve procedures at our institution during 1976 through 1987 revealed significant differences in some preoperative characteristics of the three groups analyzed. These differences were probably inevitable given the intrinsic natural stratification of the large and inclusive patient population involved. For example, patients having reoperation after a previous MVR are more likely to be in a higher-risk

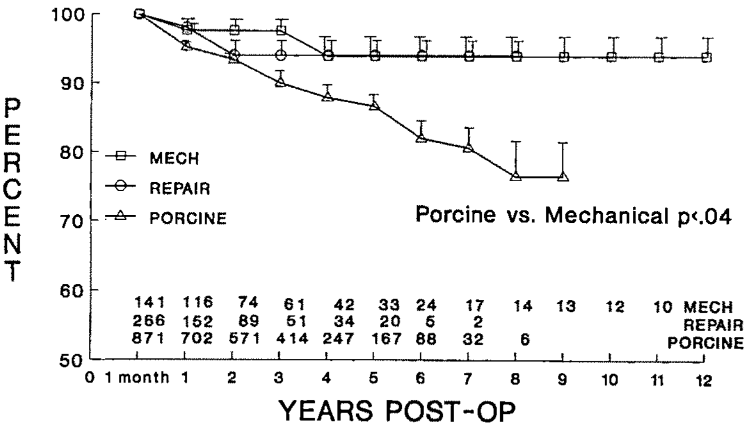
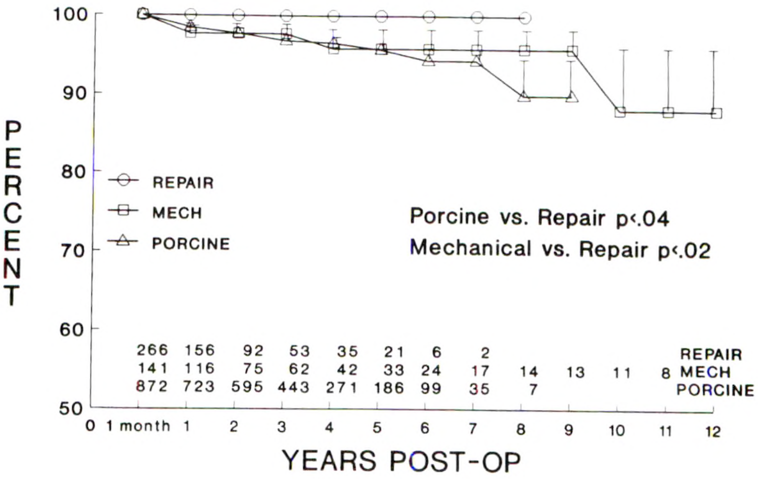


Fig 5. Actuarial freedom from late thromboembolic complications after mitral valve repair and mitral valve replacement.

Fig 6. Actuarial freedom from late endocarditis after mitral valve repair and mitral valve replacement.



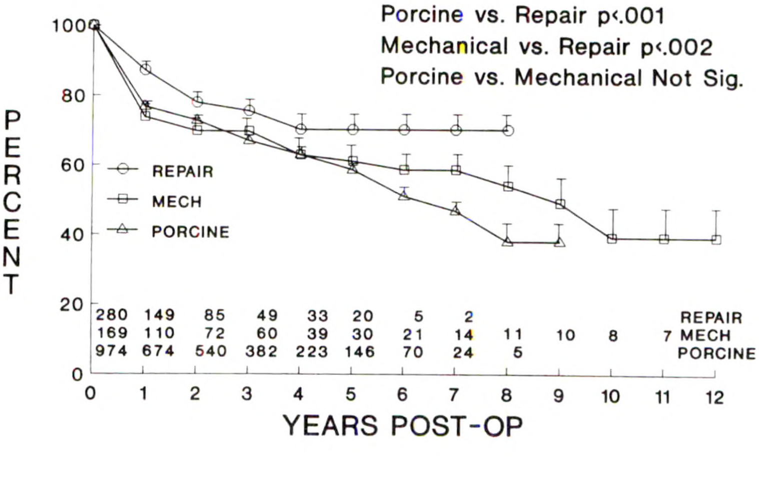
NYHA functional class than patients undergoing a mitral valve procedure for the first time, yet such patients are suitable only for another mitral replacement procedure. When attempting to test the influence of these preoperative differences by multivariate analysis, we found that the lower operative mortality noted in our valve reconstruction patients could be accounted for based on patient selection and the presence of associated risk factors. Valve repair in itself was not shown to confer a decreased operative risk.

Likewise, others [13, 14] have suggested that valve repair is associated with a lower late mortality than valve replacement. Sand and associates [15] noted an overall 5-year survival of 76% after valve reconstruction compared with a 56% 5-year survival after valve replacement done during the same time interval. Multivariate analysis of those patients revealed that type of procedure was unlikely to be predictive of late survival, which is similar to our findings. Multivariate analysis of our results indicated that among the predictors of increased operative risk and decreased late survival were age, NYHA class IV status, previous cardiac operation, and performance of concomitant cardiac surgical procedures. The type of valve procedure did not appear to influence operative risk or late survival when the results for the three groups were corrected for associated risk factors.

A concern limiting widespread acceptance of mitral valve reconstruction has been the uncertain durability of this procedure. We [10] previously reported excellent functional durability after valve reconstruction with follow-up echocardiographic studies in 83% of our patients. In that report, we noted a trend toward a higher valve failure rate in the rheumatic population. Carpentier [4, 5], Duran [16], Antunes [17], and their associates have all reported notable valve failure rates in rheumatic populations undergoing valve reconstruction. Our current data confirm that rheumatic patients undergoing valve reconstruction have a higher valve failure rate than both nonrheumatic patients undergoing valve reconstruction and patients undergoing MVR. Conversely, nonrheumatic patients having valve reconstruction have a 5-year freedom from reoperation equivalent to that obtained in patients with either mechanical or porcine prostheses. In addition, the late instantaneous risk of valve failure is uniformly low for the valve reconstruction group. This is in sharp contrast to the rising late risk of valve failure noted after porcine valve replacement, results similar to those published by Sand and the Alabama group [15].

Many reports have demonstrated a striking freedom from late thromboembolism in valve reconstruction patients, despite the absence of routine anticoagulation [4, 5, 10, 11, 13, 18–20]. The approximately 95% 5-year freedom

Fig 7. Actuarial freedom from all cardiac-related morbidity and mortality (complication-free survival from cardiac death) after mitral valve repair and mitral valve replacement. (Sig. = *significant.)*



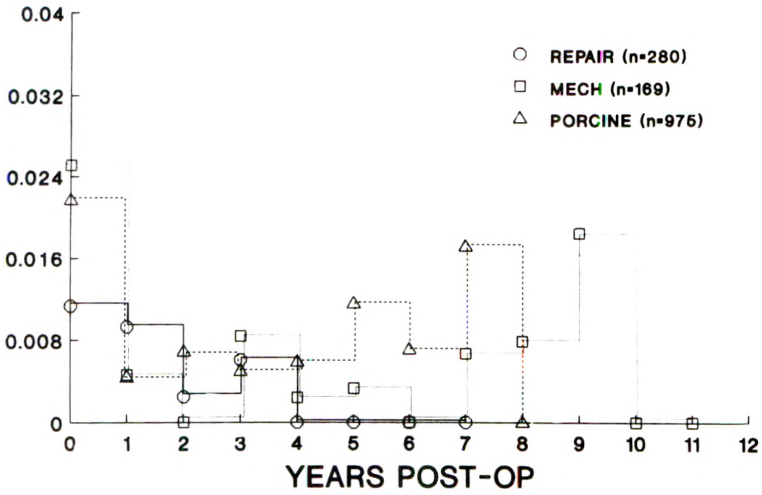


Fig 8. Interval hazard rate for all cardiac-related morbidity and mortality after mitral valve repair and mitral valve replacement.

from thromboembolism after valve reconstruction reported by most authors [4, 5, 10, 11, 13, 18–20] contrasts markedly with the 5-year freedom from thromboembolism of 65% to 90% reported in most prosthetic valve series [3].

In this study, we demonstrated a 94% 5-year freedom from thromboembolism without extensive use of warfarin therapy in our patients receiving valve reconstruction. However, 94% of the mechanical valve patients also remained free from thromboembolism at 5 years. A contributing factor to this result may be that we frequently select our most compliant patients to undergo mechanical valve replacement, thus often reserving the procedure for those who have previously demonstrated reliability with respect to adherence to a warfarin regimen. Nevertheless, anticoagulant-related complications remain a constant risk in patients undergoing MVR, whereas the risk of anticoagulant-related complications appears negligible after valve reconstruction.

In the liaison committee's recommendations for reporting valve-related morbidity [12], it was proposed that a useful method of valve morbidity analysis is the combination of all valve-related morbidity and mortality. This combination includes all operative deaths, all late valve-related deaths, and all nonfatal valve-related morbid events. When reported in this fashion, our data clearly show that patients undergoing valve reconstruction have less combined valve-related morbidity than patients undergoing valve replacement. Furthermore, the late instantaneous risk of sustaining a valve-related morbid event remains higher for valve replacement patients.

In conclusion, the present results show mitral valve reconstruction to be as safe as MVR with respect to operative risk and late survival. Nonrheumatic patients undergoing mitral valve reconstruction have a late valve durability equivalent to that noted after mechanical or porcine valve replacement. However, freedom from all valve-related combined morbidity and mortality is significantly better after valve reconstruction than after valve replacement, thus making mitral valve reconstruction the preferred operative procedure for many patients with mitral insufficiency.

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Discussion

DR L. HENRY EDMUNDS, JR (Philadelphia, PA): Although I did not have an opportunity to review the manuscript, I will make some comments based on the abstract and on Dr Galloway's excellent presentation.

Dr Galloway pointed out that the abstract and presentation differ in that they have excluded from the presentation the nonconcurrent series of Starr-Edwards mechanical valves and focused on a concurrent series. I think that is an important change if we are going to compare reconstruction, porcine valves, and mechanical valves in the mitral position.

I note that less than a quarter of the patients had reconstructed valves; this represents a select cohort of patients. This is a very important fact because the people who receive porcine and mechanical valves are residuals of the selection process. Therefore, it is not surprising to find operative mortality a little less for reconstruction as it was in the abstract.

Halseth, Carpentier, Cosgrove, and others all attest to the reduced rate of thromboembolism and bleeding complications of reconstructed mitral valves compared with prosthetic mitral valves. In a review published last year, the thromboembolic and bleeding complications of various mechanical valves do not differ much from those of Hancock valves.

The main reservation that I have about reconstructed valves is durability. If the selection criteria for reconstruction are stringent, the valve repair is likely to be excellent and the durability will probably be good, so that at 10 or more years the reoperation rate will be low. However, if the criteria are rather liberal, fewer good functional valves will result, and it is likely that the valve will need to be replaced or reoperated on within a 10-year period. In Dr Galloway's presentation, mean follow-up of reconstructed valves was only 22.5 months. Thus, anything beyond about 3 or 4 years must be based on a small number of patients.

I see little reason to insert a bioprosthesis in the mitral position except in very special circumstances. The choice is between reconstruction and a mechanical prosthesis. Reconstruction is best if you can produce a well-functioning valve that is likely to last longer than the patient. If not, I prefer a bileaflet mechanical prosthesis.

DR GALLOWAY: Thank you, Dr Edmunds. I agree with your comments entirely. Certainly, repair durability has been the prime concern of everyone when considering mitral valve reconstruction. The 5-year freedom from reoperation in this study is 94.4% for all nonrheumatic patients undergoing valve reconstruction, but only 77.4% for rheumatic patients undergoing valve reconstruction. We have also performed follow-up pulse and color Doppler echocardiography in 82% of our patients, with a mean echocardiographic follow-up of 27 ± 21 months. Overall, 93% of our patients remain without major echocardiographic evidence of recurrent mitral insufficiency. When we define valve durability after mitral valve reconstruction as the combined freedom from late valve replacement and freedom from major echocardiographic evidence of valvular insufficiency, the nonrheumatic patients continue to show excellent repair durability, 94% at 5 years. In contrast, the rheumatic patients continue to show major problems with valve durability, with only 70% remaining without major valve failure at 5 years.

The ramifications of this study are important. First, we were surprised at the extremely good late results after mechanical MVR. Patients receiving a mechanical valve prosthesis had no more complications and had fewer reoperations than patients receiving a porcine valve prosthesis, although we may have biased the results somewhat by choosing our most compliant patients for mechanical valves. Clearly, some of our older rheumatic patients should not have undergone valve reconstruction. Avoidance of valve reconstruction in this group should improve the overall durability of the procedure. We are now closely evaluating our patient selection criteria for valve reconstruction in the rheumatic population, and we will be more selective with reconstruction in this group in the future. However, these data clearly demonstrate that valve reconstruction in nonrheumatic patients is extremely durable. Furthermore, patients undergoing valve reconstruction have fewer valve-related complications and fewer valve-related deaths than patients undergoing valve replacement. Thus, we think mitral valve reconstruction is the operative procedure of choice for nonrheumatic patients with mitral insufficiency.

Myocardial Adenine Nucleotide Metabolism in Pediatric Patients During Hypothermic Cardioplegic Arrest and Normothermic Ischemia

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Quantitative assessment of high-energy phosphate levels, including degradation or utilization during ischemia, has not previously been performed in infants and children. Animal experiments suggest that high-energy phosphate metabolism varies with maturation. To help answer these questions, 24 patients aged 2 months to 8 years underwent myocardial biopsy immediately after the institution of cardiopulmonary bypass (16 to 20°C). Additional samples were obtained at 16 and 45 minutes after aortic cross-clamping and administration of cardioplegia (St. Thomas's solution) (in vivo ischemia). Seven patients also underwent major myocardial resection. Resected specimens were placed in a 37°C bath and divided into equal-sized samples that were removed at ten-minute intervals (in vitro ischemia). All samples were immersed in liquid nitrogen and analyzed for adenine nucleotide pool metabolites using high-performance liquid chromatography. Levels of adenosine triphosphate were high before cross-clamping but diminished during the period of protected ischemia. Adenosine triphosphate loss was much more pronounced in patients less than 18 months old ($p < 0.05$) and was associated with accumulation of adenosine monophosphate and inosine, a finding not seen in patients more than 18 months old ($p < 0.05$). The same trends documented during in vivo ischemia were noted during in vitro ischemia. Immaturity of 5'-nucleotidase results in accumulation of adenosine monophosphate during ischemia. It is known that 5'-nucleotidase is present in neonatal myocardial cell membranes and absent from the cytosol. Our findings suggest that a relative deficiency of cytosolic 5'-nucleotidase exists beyond the neonatal period and also that the myocardium of patients less than 18 months of age is not adequately protected by both hypothermia and the cardioplegic solution used in this study.

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During the past decade, major advances have been made that extend fundamental observations in myocardial metabolism in such a way as to bring new knowledge into direct clinical application [1]. Controlled circumstances in a bloodless field with unimpaired visualization directly affect the technical performance of cardiac surgical procedures, which must be reflected in results. This is especially true in congenital cardiac procedures, where the size of the field is small, technical demands considerable, and time limited. The price one pays for a bloodless, immobile operative field is myocardial ischemia.

Despite extraordinary advances in cardiac surgery for infants and children with congenital heart defects, operative morbidity and mortality remain high for repair of many defects. Diminished ventricular function is a principal determinant of outcome in these patients [2, 3].

An important correlate of myocardial function after ischemia is the level of adenosine triphosphate (ATP). The high-energy phosphate bond of ATP serves as the main energy source for myocardial contraction [4]. Levels of ATP relate closely to myocardial function before, during, and after periods of ischemia [3, 5, 6]. Likewise, interventions that replenish adenosine nucleotides after ischemia have been demonstrated to improve myocardial functional recovery after ischemia [7, 8]. A working knowledge of adenine nucleotide metabolism during ischemia and of avenues of repletion during reperfusion is essential in designing metabolic interventions that may improve recovery after ischemia.

Several studies [3, 9] have addressed specifically the problem of myocardial protection in children. Quantitative assessment of high-energy phosphate stores has also been performed in a variety of laboratory animals [10, 11]. Likewise, manipulation of substrates necessary to generate high-energy phosphates has been performed with documentation of improvement in myocardial recovery of ATP stores [1, 7, 8]. Little, however, has been done to quantitatively assess baseline, ie, preischemic high-energy phosphate levels in neonates, infants, and children. Similarly, a quantitative assessment of high-energy phosphate degradation or utilization after periods of ischemia has also not been performed. There are sugges-

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tions that high-energy phosphate metabolism may vary with maturation. Confirmation of this in human myocardium may directly affect measures taken to provide myocardial protection during ischemia. The present study was undertaken to address these issues.

Material and Methods

Twenty-four patients aged 2 months to 8 years underwent myocardial biopsy immediately after the institution of cardiopulmonary bypass. Biopsy specimens were obtained using a Tru-cut needle. Additional biopsy specimens were obtained after aortic cross-clamping and administration of cold St. Thomas's Hospital cardioplegic solution. All specimens were rapidly immersed in liquid nitrogen within seconds of acquisition. Perfusion was carried out in all patients at a temperature of 16° to 20°C. Seven patients also underwent major myocardial resection for relief of ventricular outflow tract obstruction. All resected myocardium was rapidly placed in a 37°C bath of normal saline solution and divided into equal-sized specimens. Specimens were removed at ten-minute intervals after immersion and placed in liquid nitrogen.

The baseline sample throughout the study is defined as the sample obtained immediately after institution of cardiopulmonary bypass on an empty, beating heart. For in vitro data, the time 0 sample is defined as the first sample obtained after myocardial resection. Myocardial resection was accomplished between 11 and 19 minutes after aortic cross-clamping and administration of cardioplegic solution.

Informed consent for the protocol was obtained through the Standing Committee on Ethical Practice, The Hospital for Sick Children/Queen Elizabeth Hospital, and Institute of Child Health, University of London.

Chemical Reagents

Standard enzymes and ultrapure biochemical buffers and reagents were purchased from Sigma Chemical Company (St. Louis, MO). High-performance liquid chromatography–grade ammonium phosphate and methanol were obtained from Fisher Scientific (Fair Lawn, NJ). Organic-free deionized water was obtained from a Milli-Q system (Millipore, Bedford, MA).

High-Performance Liquid Chromatography System

Standard solutions of a mixture of adenine nucleotides, nucleosides, purine bases, nicotinamide adenine dinucleotide (NAD^+), and cyclic adenosine monophosphate (cAMP) or unknown samples were injected by a Waters intelligent sampler processor (model 710B; Waters Associates, Milford, MA). A solvent selector (model 101; All Tech Association, Dearfield, IL) was used in conjunction with the solvent delivery system (model 6000A; Waters Associates). Separation of these metabolites was accomplished through a NOVA-PAK-A (C18, 5-μm particle size, 10 × 8 mm) chromatographic column inside a radial compressor (model RCM 100; Waters Associates). A multiwavelength four-channel visible/ultraviolet detector (model 490) and a data module (model 730; Waters Associates) were used to detect, integrate, and quantitate eluted metabolites using external standards.

Table 1. Adenine Nucleotide Metabolites During Cardioplegic Arrest[a]

	Length of Arrest (min)		
Variable	0	16	45
ATP	26.95 ± 2.9	19.72 ± 5.1[b]	16.64 ± 9.5[b]
ADP	12.67 ± 0.76	11.07 ± 0.87	9.98 ± 1.05
AMP	6.20 ± 3.2	6.02 ± 2.0	7.22 ± 3.5
Adenosine	0.57 ± 0.21	1.1 ± 0.24	1.7 ± 0.29
Inosine	0.13 ± 0.3	1.90 ± 1.6[b]	6.00 ± 4.2[b]
Hypoxanthine	0.03 ± 0.1	0.34 ± 0.1	0.4 ± 0.13
Xanthine	0.01 ± 0.07	0.25 ± 0.08	0.36 ± 0.1
NAD^+	5.06 ± 0.33	3.71 ± 0.38[b]	3.5 ± 0.46[b]
Cyclic AMP	0.26 ± 0.18	0.88 ± 0.21[b]	0.34 ± 0.25
TAN	40.11 ± 2.52	36.69 ± 2.88	31.03 ± 3.46
TDN	1.14 ± 0.69	3.75 ± 0.79[b]	7.13 ± 0.95[b]
TDP	1.26 ± 0.79	4.35 ± 0.91[b]	7.89 ± 1.09[b]
Cell energy charge	20.76 ± 2.01	19.7 ± 2.3	14.01 ± 2.76

[a] Data are shown as the mean ± the standard error of the mean in nanomoles per milligram of protein. [b] Significance: $p < 0.05$ compared with baseline value.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; NAD^+ = nicotinamide adenine dinucleotide; TAN = total adenine nucleotides; TDN = total diffusible nucleosides; TDP = total diffusible purines.

High-Performance Liquid Chromatography Analysis

A step-gradient elution of adenine nucleotides, nucleosides, purine bases, NAD^+, and cAMP was performed as previously described [12]. Briefly, high-performance liquid chromatography–grade ammonium phosphate buffer, pH 5.5 (adjusted with 0.6 N ammonium hydroxide), elutes sequentially ATP, adenosine diphosphate (ADP), hypoxanthine, xanthine, and AMP. As a second solvent, 7% methanol elutes NAD^+, and a third solvent, 40% methanol, elutes inosine, cAMP, and adenosine. Switching the solvent selector is programmed in the data module [12].

Statistical Analysis

Data are presented as the mean ± the standard error of the mean. Student's t test for unpaired data was used to determine significant differences at discrete periods of study. Sequential measurements were compared with repeated-measures analysis of variance with SAS software (Statistical Analysis Systems, Cary, NC). Differences were considered significant if the probability value of comparison of least squares means was less than 0.05.

Results

In Vivo Data

Table 1 summarizes in vivo (protected ischemia) data for the entire population of patients. Levels of ATP were high before cross-clamping but diminished throughout the period of hypothermic cardioplegic arrest. The ATP levels at 16 and 45 minutes of protected ischemia were signifi-

Table 2. Baseline Values of Adenine Nucleotide Metabolites During Cardioplegic Arrest by Age Group[a]

Variable	Older than 18 Months	18 Months or Younger
ATP	28.55 ± 0.35	26.29 ± 3.05
ADP	10.49 ± 0.82	12.15 ± 0.65
AMP	5.29 ± 0.72	7.53 ± 0.57[b]
Adenosine	0.56 ± 0.23	1.29 ± 0.18[b]
Inosine	1.80 ± 0.74	2.75 ± 0.58
Hypoxanthine	0.09 ± 0.11	0.31 ± 0.09
Xanthine	0.30 ± 0.08	0.15 ± 0.06
NAD^+	4.24 ± 0.40	4.26 ± 0.31
Cyclic AMP	0.57 ± 0.21	0.44 ± 0.16
TAN	35.11 ± 2.78	37.98 ± 2.20
TDN	2.37 ± 0.93	4.04 ± 0.74
TDP	2.76 ± 1.06	4.49 ± 0.84
Cell energy charge	19.48 ± 2.23	18.46 ± 1.76

[a] Data are shown as the mean ± the standard error of the mean in nanomoles per milligram of protein. [b] Significance: $p < 0.05$ between age groups.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; NAD^+ = nicotinamide adenine dinucleotide; TAN = total adenine nucleotides; TDN = total diffusible nucleosides; TDP = total diffusible purines.

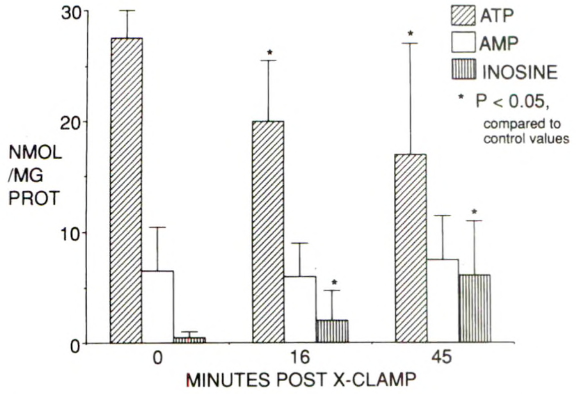

Fig 1. Data on adenine nucleotide metabolites during protected ischemia for the entire group of patients. Note the fall in adenosine triphosphate (ATP) levels and rise in inosine levels during the period of cardioplegic arrest. (AMP = adenosine monophosphate; PROT = protein; X-CLAMP = aortic cross-clamping.)

cantly different from control levels, however. There was no significant difference between ATP levels at 16 minutes versus 45 minutes of protected ischemia.

There were no significant differences in ADP, AMP, or adenosine levels during the period of cardioplegic arrest. Baseline inosine levels were quite low and rose progressively and significantly throughout the period of protected ischemia. Hypoxanthine and xanthine levels were low before protected ischemia and remained low, with no significant difference detected. Levels of NAD^+ declined significantly throughout the test period. Cyclic AMP levels increased significantly at 16 minutes of protected ischemia and then returned to near baseline levels at 45 minutes. Total adenine nucleotide levels were never significantly different from control levels. Total diffusible nucleoside levels and total diffusible purine levels rose progressively throughout the period of protected ischemia.

The data in Table 2 demonstrate that baseline values for adenine nucleotide pool metabolites were similar for both age groups of patients. The exceptions were AMP and adenosine, both of which were significantly higher in the younger group.

Figure 1 illustrates the progressive fall in ATP levels that occurred during the period of ischemia. Levels of AMP remained relatively constant, but there was a progressive rise in inosine levels. When the total group of patients is divided into children less than 18 months old and children greater than 18 months old, the differences in adenine nucleotide metabolites become pronounced (Fig 2). Patients less than 18 months old demonstrated a marked reduction in ATP and a greater accumulation of AMP and inosine compared with those more than 18 months old.

In Vitro Ischemia

The in vitro ischemia data are summarized in Table 3. With the exception of hypoxanthine and xanthine, all adenine nucleotide pool metabolites were significantly different from their baseline values after ten minutes of normothermic ischemia. There was progressive loss of ATP and ADP, with associated progressive accumulation of diffusible metabolites, principally inosine. Figures 3 through 5 illustrate the age-related differences in ATP, ADP, AMP, and inosine that occurred over the period of normothermic ischemia. Of note is the fact that ATP levels were higher in older children for the first 20 minutes of ischemia, whereas AMP and inosine levels tended to be higher in the younger group after 20 minutes of ischemia. The number of patients in the group undergoing myocardial resection was quite small, thereby making stratifica-

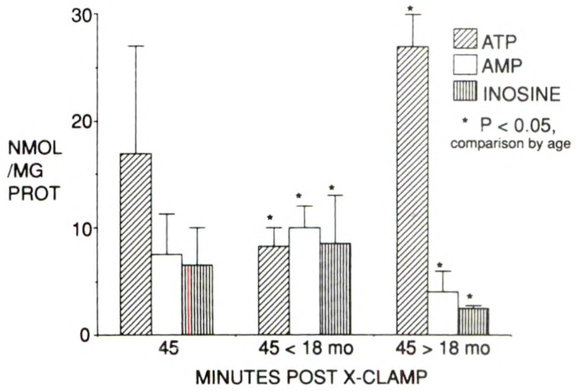

Fig 2. Data on adenine nucleotide metabolites at 45 minutes of protected ischemia for the entire group of patients divided into two age groups. Note the significant difference in adenosine triphosphate (ATP), adenosine monophosphate (AMP), and inosine levels between the two groups. (PROT = protein; X-CLAMP = aortic cross-clamping.)

Table 3. Adenine Nucleotide Metabolites During In Vitro Ischemia[a]

	Time[b]							
Variable	0	10	20	30	40	50	60	120
ATP	17.19 ± 3.07	6.38 ± 1.33	8.36 ± 3.54	4.58 ± 0.89	2.25 ± 0.71	1.49 ± 0.57	4.40 ± 1.87	2.04 ± 0.34
ADP	12.03 ± 1.14	6.89 ± 0.69	6.58 ± 1.40	6.27 ± 0.37	3.70 ± 0.52	2.93 ± 0.94	5.07 ± 1.14	2.60 ± 0.13
AMP	7.95 ± 0.95	11.76 ± 2.20	5.57 ± 1.61	10.00 ± 1.45	6.35 ± 1.62	4.33 ± 1.64	9.65 ± 3.45	6.76 ± 1.61
Adenosine	1.10 ± 0.28	2.73 ± 0.22	1.51 ± 0.51	1.09 ± 0.28	0.46 ± 0.11	0.27 ± 0.14	0.70 ± 0.31	0.00 ± 0.00
Inosine	1.96 ± 0.43	6.78 ± 1.09	10.57 ± 2.63	9.82 ± 1.52	5.34 ± 1.00	5.24 ± 1.20	9.14 ± 1.23	4.16 ± 0.24
Hypoxanthine	0.30 ± 0.12	0.43 ± 0.28	0.76 ± 0.36	0.84 ± 0.50	0.35 ± 0.14	0.53 ± 0.30	0.51 ± 0.25	0.00 ± 0.00
Xanthine	0.22 ± 0.12	0.15 ± 0.06	0.21 ± 0.14	0.20 ± 0.09	0.24 ± 0.11	0.36 ± 0.17	0.91 ± 0.61	0.00 ± 0.00
NAD^+	4.22 ± 0.47	2.15 ± 0.21	2.34 ± 0.45	2.27 ± 0.30	1.55 ± 0.24	1.37 ± 0.29	2.43 ± 0.47	1.79 ± 0.05
Cyclic AMP	0.44 ± 0.11	0.64 ± 0.10	0.71 ± 0.18	0.89 ± 0.06	0.58 ± 0.03	0.58 ± 0.01	0.47 ± 0.22	0.57 ± 0.08
TAN	37.17 ± 3.24	25.02 ± 3.10	20.51 ± 5.05	20.86 ± 1.40	12.31 ± 2.44	8.75 ± 3.12	19.13 ± 4.36	11.40 ± 2.08
TDN	3.06 ± 0.61	9.51 ± 1.10	12.08 ± 3.08	10.91 ± 1.78	5.80 ± 1.04	5.51 ± 1.33	9.83 ± 1.47	4.16 ± 0.24
TDP	3.57 ± 0.64	10.09 ± 1.37	13.05 ± 3.34	11.95 ± 2.31	6.39 ± 1.09	6.39 ± 1.73	11.26 ± 1.81	4.16 ± 0.24
Cell energy charge	0.59 ± 0.05	0.39 ± 0.04	0.51 ± 0.08	0.37 ± 0.04	0.33 ± 0.03	0.32 ± 0.04	0.36 ± 0.07	0.30 ± 0.02

[a] Data are shown as the mean ± the standard error of the mean in nanomoles per milligram of protein. [b] Time 0 is the time during cardioplegic arrest when myocardial resection was performed. This occurred between 11 and 19 minutes after administration of cold cardioplegic solution. The remaining time intervals are minutes of normothermic ischemia after myocardial resection.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; NAD^+ = nicotinamide adenine dinucleotide; TAN = total adenine nucleotides; TDN = total diffusible nucleosides; TDP = total diffusible purines.

tion with statistical differences very difficult. However, the age-related trends documented during protected ischemia were noted during unprotected in vitro normothermic ischemia.

Comment

Studies have demonstrated metabolic differences in immature as opposed to adult myocardium in several animal models, and in several species [13–15]. Most of these studies compared fetal or neonatal myocardium with adult myocardium [16]. Other investigators [17] have documented age-dependent changes occurring in rat sarcolemma and their effect on calcium metabolism. It has been shown that neither hypothermia nor intermittent washout with a noncardioplegic solution is capable of adequately protecting neonatal rabbit myocardium, and that left ventricular function is improved significantly if cardioplegia is used [18]. The optimal cardioplegic solution for preservation of high-energy phosphate stores has not yet been developed. Studies have shown that current methods of myocardial protection in some congenital heart operations are inadequate for optimal preservation of short-term ventricular function [3].

Even though some clinical and laboratory studies would suggest that preservation of "immature" myocardium is suboptimal, other studies have produced con-

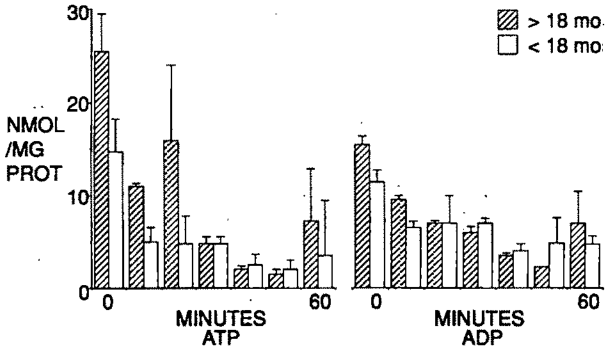

Fig 3. Representative data on adenine nucleotide metabolites during normothermic ischemia (in vitro ischemia). Time 0 is the time at which myocardial resection was performed after cross-clamping and administration of cardioplegic solution (ADP = adenosine diphosphate; ATP = adenosine triphosphate; PROT = protein.)

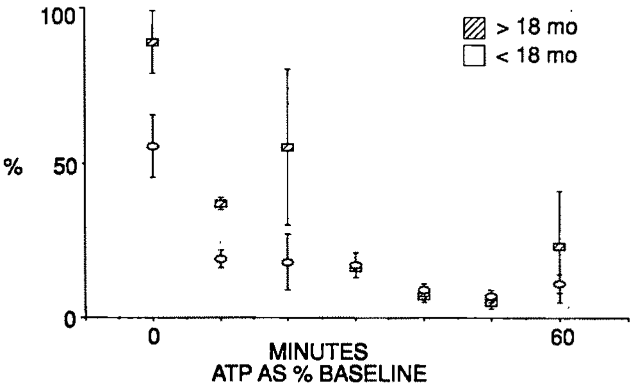

Fig 4. Normalized adenosine triphosphate (ATP) data during normothermic ischemia. Levels of ATP are expressed as a percentage of baseline, ie, preischemic values. Time 0 is the time during protected ischemia when myocardial resection was performed. Note that in the older patients, the ATP level is virtually identical to baseline at the time of myocardial resection, while in the younger patients, it has already fallen to 55% of baseline.

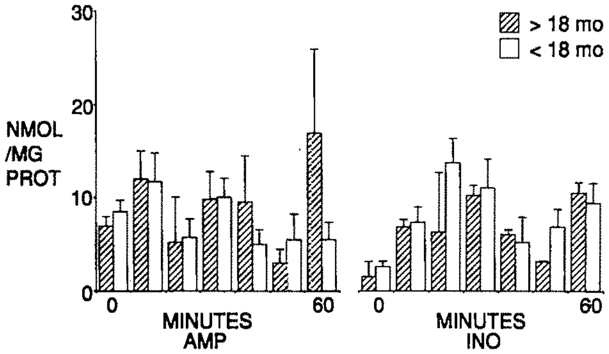

*Fig 5. Data on adenosine monophosphate (*AMP*) and inosine (*INO*) during normothermic ischemia (in vitro ischemia). Note that levels of AMP and inosine during normothermic ischemia tend to be higher in the younger group. The number of patients in each group was too small to allow for a statistical comparison.*

flicting results [13, 14]. In an isolated rat heart model, Yano and colleagues [19] utilized intraventricular balloons to study myocardial performance after periods of ischemia. Their studies suggested that the neonatal rat heart has a greater inherent tolerance for ischemia than that of the infant or adult rat. In other studies in isolated rabbit hearts, Bove and associates [20] found that neonatal rabbit hearts recovered systolic function better than the adult heart after global ischemia with moderate hypothermia.

The present study suggests that protection of human pediatric myocardium is suboptimal. None of the patients in the current study were neonates. However, we think these studies indicate that age-related differences in myocardial metabolism persist beyond the neonatal period. Previous work has demonstrated that in a canine heart model, 5′-nucleotidase, a regulatory enzyme that dephosphorylates AMP to adenosine, is present in neonatal microsomal membranes but absent from the cytosolic preparations. The finding that patients less than 18 months of age have lower levels of ATP and higher levels of AMP and inosine support laboratory findings suggesting that immature myocardium has significantly lower levels of 5′-nucleotidase than adult myocardium. Morphological studies have shown a deficiency in immature myocardial cells of T tubules, where 5′-nucleotidase is normally found to be concentrated in the adult heart [21, 22]. The current study suggests that this relative deficiency of cytosolic 5′-nucleotidase exists well beyond the neonatal period, similar to that of the canine immature myocardium [23, 24].

Baseline ATP levels are similar in younger patients (less than 18 months old) and older patients (greater than 18 months old). However, ATP levels in the younger patients declined markedly during hypothermic cardioplegic arrest (protected ischemia) using St. Thomas's solution. This may be related to damaging effects of hyperkalemia on immature myocardium [25]. The mechanisms by which potassium affects metabolic and functional recovery after ischemia in immature hearts are not known and warrant further investigation.

Although the number of patients in each group investigated in this study is small, we found similar trends of age-related differences in the effect of ischemia on adenine nucleotide degradation in canine hearts. It was noted that 5′-nucleotidase is present in neonatal myocardial cell membranes but absent from the cytosol. The finding that patients less than 18 months old have lower levels of ATP and higher levels of AMP and inosine after "protected" ischemia supports laboratory findings suggesting that immature myocardium has significantly lower levels of 5′-nucleotidase than adult myocardium. The current study suggests that this relative deficiency of cytosolic 5′-nucleotidase exists well beyond the neonatal period. This observation may be of importance because of the greater potential for AMP to participate in "salvage" recovery of ATP from inosine.

The failure to preserve ATP under conditions designed to provide good intraoperative myocardial protection is concerning. This observation affirms the hypothesis that protection of immature myocardium is not yet optimal and requires further investigation.

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DISCUSSION

DR JOHN W. HAMMON JR (Nashville, TN): Because the majority of operations for congenital heart disease are performed in patients in the first few years of life, it requires the best surgical technique and myocardial protection to ensure a good technical result and normal myocardial pump function for the many years that follow. Systematic study of these patients is quite important in analyzing changes in technique and myocardial protection. For that reason, I congratulate Dr Lofland and his co-workers for their study of adenine nucleotide metabolism in a group of patients undergoing congenital heart operations. My associates and I have also been interested in this issue, and our data are remarkably similar.

The new finding of a deficiency of 5′-nucleotidase is quite interesting and leads to the speculation that substrate enhancement with compounds such as ribose may be useful in operations for infants with congenital heart disease.

Although it would be attractive to place all the blame for high-energy phosphate loss on an enzyme deficiency and turn this problem over to the biochemists, we believe that careful concurrent examination of surgical techniques is indicated as well. In our own experience, the major factor responsible for the maintenance of high-energy phosphate stores is the use of profound hypothermia and circulatory arrest techniques during the major portion of the repair. This avoids myocardial rewarming by systemic pulmonary collaterals, which may wash out cardioplegia, leading to the need for a greater volume of potentially damaging hyperkalemic solutions. In addition, cardiopulmonary bypass is more difficult to maintain in small infants, left ventricular vents work less well, and bicaval cannulation can distort the anatomy, thus preventing an adequate technical repair. Dr Lofland, have you analyzed your series for clinical factors that may have influenced the results or for specific congenital lesions that predispose to high-energy phosphate loss?

In addition, one can point out biochemical deficiencies, but unless one correlates those with specific factors relating to ventricular function or clinical results, these biochemical data have less meaning. Have you analyzed the data for postoperative ventricular function or for the clinical result?

DR LOFLAND: I thank Dr Hammon for his comments. No attempt in this study was made to correlate these findings with either the clinical result or the ultimate outcome for the patient. Those data are available, but I am not at liberty to discuss them at this time. They will have to be analyzed further. I agree with Dr Hammon that they will provide important findings. I think that it will also be important to divide the patients in this series into cyanotic versus noncyanotic patients and to look at other clinical variables.

All patients in this series did undergo bicaval cannulation. None of the patients had periods of total circulatory arrest. Perfusion was accomplished at flow rates of approximately 1.2 L/min/m^2 at 16°C. All patients received continuous perfusion throughout the study period.

All patients had a single dose of cardioplegic solution, which was then repeated at intervals, but all of the biopsies in this study were done before administration of the second dose of cardioplegia. I think that the frequency of cardioplegia administration may have had some effect on adenine nucleotide pool metabolism; this is a variable that could also be investigated.

Preoperative Chemotherapy and Irradiation for Stage III Non-Small Cell Lung Cancer

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Surgical therapy for stage III non-small cell lung cancer (NSCLC) has not resulted in substantial long-term survival. Neoadjuvant treatment programs that could downstage the tumor and achieve increased long-term survival would be of obvious benefit. We have used preoperative simultaneous chemotherapy and irradiation in 85 patients with clinical stage III non-small cell lung cancer considered candidates for surgical resection. One group of 56 patients was treated with cisplatin, 5-fluorouracil, and simultaneoaus irradiation for five days every other week for a total of four cycles. After treatment, 39 patients underwent resection, and the operative mortality was 2 (5%) of 39. A second trial was undertaken in which etoposide (VP-16) was added because of its synergism with cisplatin. In this group, 29 patients were considered to have potentially resectable disease, and 23 underwent thoracotomy with 1 operative death (4%). Of the total of 62 patients having thoracotomy, 60 underwent resection (97%). Complications were major, and there were four bronchopleural fistulas. For the 85 patients eligible for surgical intervention in these two groups of patients, the Kaplan-Meier median survival estimate is 40% at 3 years. The median survival of the 62 patients having thoracotomy is 36.6 months. Combination preoperative chemotherapy and irradiation is feasible with acceptable toxicity and operative mortality in patients with clinical stage III non-small cell lung cancer. Prospective randomized studies are suggested for further evaluation of this treatment program.

(Ann Thorac Surg 1989;47:669–77)

Surgical resection remains the most effective therapy for non-small cell lung carcinoma (NSCLC), but the 5-year cure rate for patients with clinical stage III disease undergoing resection remains at 8% to 10%. Innovative methods of therapy are needed if we are to improve present results. Any program of preoperative therapy that will increase the incidence of curative resection and decrease the incidence of future metastatic disease would be of substantial benefit.

The concept of preoperative therapy for locally advanced NSCLC is appealing, and there are several mechanisms by which neoadjuvant therapy may be effective. The well-oxygenated neoplastic cells at the periphery of the tumor are most sensitive to irradiation and chemotherapy. By using these therapies preoperatively, the tumor can actually be downstaged, permitting a wider tumor-free resection margin or a more limited resection such as sleeve lobectomy instead of pneumonectomy. Palliative or incomplete resections should be decreased, as the edge of the tumor is frequently closely dissected from major intrathoracic structures. Hematogenous spread and local seeding of the neoplasm by surgical manipulation can theoretically be minimized by preoperative therapy, and chemotherapy can also possibly control micrometastatic disease already established. The disadvantages of any form of preoperative therapy include a delay in operation if the tumor is not responsive, death or severe toxicity from the preoperative treatment program, and an increase in postoperative complications.

Radiation therapy can be used with chemotherapy either to enhance the effect of the alternate method or to treat separate components of the malignancy, ie, local disease and microscopic metastatic disease. Irradiation and chemotherapy work similarly to effect biological tumor cell destruction, and these modes of therapy can be used in combination for the following purposes: (1) to increase the effect of the other method in the instance of bulky localized disease, (2) to accelerate response, and (3) to increase the effect of the other method in the instance of marginally responsive tumors.

Byfield and colleagues [1] combined 5-fluorouracil (5-FU) with irradiation in patients with localized NSCLC and developed an alternate-week schedule to enable the simultaneous administration of chemotherapy and irradiation. The combination of cisplatin and 5-FU infusion has been demonstrated to be synergistic in its action, giving a high response rate in locally advanced squamous cell carcinoma of the head and neck [2, 3]. Combining these agents with irradiation is appealing, as both drugs are radiation sensitizers [4]. Based on these reports, Taylor and associates [5] used a preoperative program of simultaneous cisplatin–5-FU infusion and split-course irradiation in patients with head and neck cancer. The initial results demonstrated improved regional control, and we subsequently elected to expand this program for lung cancer. Our purpose was to attempt to improve the

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resectability rate and long-term survival in patients with clinical stage III NSCLC.

Etoposide (VP-16) was added to the preoperative regimen of 5-FU plus cisplatin and irradiation because it and cisplatin produced the highest 1-year survival rate observed in a series of combination chemotherapy regimens evaluated in randomized trials in patients with stage IV NSCLC [6]. In addition, VP-16 and cisplatin have been shown to be synergistic in vitro [3].

Material and Methods

There were 130 patients with biopsy-proven clinical stage III NSCLC who were initially evaluated for a treatment program of combination chemotherapy and irradiation followed by surgical resection. There were two separate phase II studies. The first study consisted of cisplatin–5-FU infusion and split-course irradiation; in the second, VP-16 was added.

Patients were staged with computed tomography of the brain, chest, and upper abdomen and bone scans. Pleural effusions were evaluated cytologically, and if they were found to be positive, the patient was eliminated from the study. Patients were accepted into the study if there was no evidence of distant metastatic disease and they had clinical stage III NSCLC as evidenced by (1) gross mediastinal involvement by primary tumor extension or a mediastinal lymph node greater than 2 cm in diameter on computed tomographic scan, thoracotomy, or mediastinoscopy; (2) a tumor in the mainstem bronchus less than 2 cm from the carina; (3) tumor involvement of the carina or tracheobronchial angle; or (4) chest wall invasion. At the beginning of the study, each patient was evaluated by the surgical team, and a decision was made as to whether the patient was eligible for the surgical phase of the treatment program. Other eligibility requirements included Eastern Cooperative Oncology Group [7] performance status 3 or better, leukocyte count greater than 4 × 10^3/mL, platelet count greater than 100 × 10^3/mL, blood urea nitrogen value less than 25 g/dL, and bilirubin level less than 1.5 mg/dL. The Eastern Cooperative Oncology Group performance status is graded as follows:

0: Fully active; able to carry on all activities performed before disease without restriction (Karnofsky 90–100).
1: Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work (Karnofsky 70–80).
2: Ambulatory and capable of all self care, but unable to carry out any work activities; up and about more than 50% of waking hours (Karnofsky 50–60).
3: Capable of only limited self care; confined to bed or chair more than 50% of waking hours (Karnofsky 30–40).
4: Completely disabled; cannot carry on any self care; totally confined to bed or chair (Karnofsky 10–20).

The initial phase II study consisted of four cycles of combination chemotherapy and split-course irradiation administered every other week for five days. On day 1, cisplatin (60 mg/m^2/day) was given over 15 minutes with hydration, followed by 5-FU (800 mg/m^2/day) as a 24-hour infusion for five days. A radiation dose of 2 Gy was given each day during each of the four cycles. A total dose of 240 mg/m^2 for cisplatin, 16 g/m^2 for 5-FU, and 40 Gy of radiation therapy was planned to be delivered over 7 weeks.

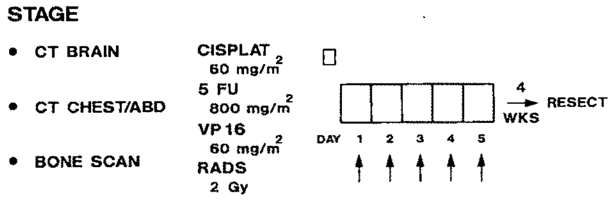

Fig 1. *Schedule for neoadjuvant chemotherapy and radiation therapy. The cisplatin* (CISPLAT)*–5-fluorouracil* (5-FU) *infusion was given on alternate weeks, and when etoposide* (VP-16) *was added, it was given every third week.* (ABD = *abdomen;* CT = *computed tomography;* RESECT = *resection.*)

In the second phase II study, VP-16 (60 mg/m^2 intravenously over 30 minutes on days 1 through 4) was added to the chemotherapy protocol. The interval between each cycle in this group was increased to 14 days to minimize hematological cytotoxicity. The 5-FU and VP-16 doses were modified for hematological cytotoxicity during the treatment program, and cisplatin was modified for renal toxicity. All three drugs were reduced for moderate to severe nausea and vomiting.

Surgical resection was carried out 4 to 5 weeks after completion of the last cycle. Before operation, patients had repeat bone, brain, and liver scans to rule out metastatic disease. Repeat bronchoscopic examination was always done to evaluate planned resection margins (Fig 1).

Results

One hundred thirty patients were evaluated for this program of combined chemotherapy and radiation therapy; 85 were considered eligible for operation. Forty-five patients were not considered candidates for surgical intervention because of insufficient cardiopulmonary reserve (16), contralateral and supraclavicular lymph node metastases (15), and extensive mediastinal disease as evidenced by vena caval obstruction or extensive tracheal or carinal involvement (14).

Combined Treatment Groups

From November 1982 through December 1985, 64 patients were evaluated for entrance into the two-drug (cisplatin and 5-FU) and simultaneous irradiation preoperative treatment program. There were 56 patients determined to be eligible for operation. Between April 1985 and September 1987, 66 patients were evaluated for the three-drug (cisplatin, 5-FU, and VP-16) and simultaneous irradiation program, and 29 were determined to be eligible for surgical intervention. Of the 85 patients considered to be surgical candidates, 57 were male and 28, female. Histology was squamous in 39, adenocarcinoma in 29, and large

Table 1. Clinical Staging

Stage	No. of Patients	Method of Staging	No. of Patients
T3 N2	34	Mediastinoscopy	29
T2 N2	25	CT scan	29
T1 N2	3	Vocal cord paralysis	3
		Thoracotomy	1
T3 N0	18	Chest wall invasion	9
		CT scan	6
		Bronchial involvement	3
T4 N0	2	Tracheal/Carinal involvement	4
T4 N2	3	Thoracotomy	1

CT = computed tomographic.

Table 3. Surgical Procedures

Procedure	No. of Patients[a]
Pneumonectomy	24 (39)
Lobectomy[b]	23 (37)
Sleeve lobectomy	6 (10)
Segmentectomy	7 (11)
Unresectable	2 (3)

[a] Numbers in parentheses are percentages. [b] Three were bilobectomies.

cell in 17. The Eastern Cooperative Oncology Group performance status was 1 or less in 73 patients and 2 or 3 in 12 patients.

Staging is outlined in Table 1. A total of 62 patients had clinical N2 disease, of whom 29 had histological confirmation by mediastinoscopy. Twenty-nine had mediastinal lymph node involvement by computed tomographic scan with nodes greater than 2.0 cm in diameter, and 3 had vocal cord paralysis; in 1, thoracotomy was used for staging. Eighteen patients had T3 N0 disease, of whom 9 had chest wall invasion, 6 demonstrated mediastinal involvement with obliteration of adjacent fascial planes on the computed tomographic scan, and 3 had mainstem bronchial disease less than 2 cm from the carina. Five patients were classified as having T4 disease by demonstration of extension to the right tracheobronchial angle in 4 and to the carina in 1. Table 2 compares the preoperative clinical staging with the surgical pathological staging of the 62 patients who did undergo thoracotomy.

Eighty patients completed the full four cycles of therapy. Five patients failed to receive the planned four cycles because of the development of metastasis during therapy (3), severe nausea and vomiting (1), and death related to treatment (1). This last patient died of sepsis with a white blood cell count of 100/mL. The median white blood cell count nadir was 3.3×10^3/mL, and the median platelet nadir was 217×10^3/mL. Nausea and vomiting was commonly associated with the chemotherapy, and was mild in 24 patients, moderate in 25 and severe in 15; in 21 patients it did not occur. If nausea and vomiting was severe, drug doses were modified. Of the 85 patients eligible for operation, 2 died of documented myocardial infarction during therapy. Mild to moderate radiation dermatitis occurred in 8 patients; moist desquamation of the skin did not occur. Severe radiation esophagitis occurred in 3 patients. Alopecia developed in all patients who received VP-16, and all 85 patients complained of fatigue.

Surgical Group

Sixty-two patients (73%) had a thoracotomy after the combined treatment therapy. The reasons for not undergoing operation were refusal (13), progression of disease while on treatment (7), death from myocardial infarction during treatment (2), and death from treatment (1). The surgical procedures performed are listed in Table 3. There were six sleeve lobectomies, indicating a possible down-

Table 2. Comparison of Preoperative Clinical Staging and Surgical Pathological Staging

Clinical Stage	Surgical Pathological Stage							
	T0 N0	T1 N0	T1 N2	T2 N0	T2 N2	T3 N0	T3 N2	T4 N2
T1 N2 (n = 1)	0	0	1	0	0	0	0	0
T2 N2 (n = 17)	3	4	4	2	3	0	1	0
T3 N0 (n = 17)	5	2	1	2	0	7	0	0
T3 N2 (n = 23)	8	4	3	0	2	0	6	0
T4 N0 (n = 2)	1	0	0	0	0	0	0	1
T4 N2 (n = 2)	0	1	0	0	0	0	0	1

Table 4. Surgical Results[a]

Results	No. of Patients
Death	3/62 (5)
Resection	60/62 (97)
Complications	14
Fistula	4
Tracheostomy	2
Atelectasis	5
Pneumonitis	2
Stroke	1
Alive/NED	25/62 (12 to 62 mo)
Alive/disease	5/62 (5 to 44 mo)

[a] Numbers in parentheses are percentages.

NED = no evidence of disease.

staging of bulky hilar disease. Segmental resection was carried out in 6 patients who had chest wall involvement and in 1 patient who had no evidence of residual disease at the time of resection. In 2 patients, the disease was deemed unresectable, although in 1, biopsy specimens of firm fibrotic mediastinal disease were negative for microscopic cancer. This patient remains alive and free from disease 55 months after the initiation of therapy. The resectability rate was 97% (60/62).

The operative mortality was 5% (3/62); all 3 patients who died had pneumonectomy. Two postoperative deaths were due to pulmonary emboli, and 1 was caused by pulmonary infection in the remaining lung. Major complications occurred in 14 patients. Four had a bronchopleural fistula. The bronchial fistula occurred in 3 patients after pneumonectomy and in 1 patient after bilobectomy. In all but one of the resections, the bronchial stump was closed by stapling techniques. Other major complications included tracheostomy (2), prolonged and severe atelectasis (5), severe pneumonitis (2), and cerebrovascular accident (1) (Table 4).

Among the 60 patients who underwent resection, there was a positive surgical resection margin in 2. One occurred as a result of carcinoma invading the transverse aortic arch, and the other was at the edge of a chest wall resection. These patients both died of distant disease at 21 months and 28 months, respectively. Local recurrence was not a postoperative problem in their management, but both received an additional two cycles of therapy. Five patients had tumor extending to the parietal pleura and had an extrapleural dissection with the pulmonary resection. Three of these patients are alive and free from disease; 2 died of distant metastatic carcinoma.

Careful evaluation of all surgical specimens was carried out to assess pathological response in the pretreatment program. There were 17 patients who had no evidence of residual cancer in the resected lung or regional and mediastinal lymph nodes. Eleven patients had microscopic residual cancer, and 34 had gross residual cancer. Table 5 shows survival based on histological findings at operation. The method of clinical staging for the 17 patients who had no residual cancer is depicted in Table 6.

Table 5. Results Based on Histological Findings at Operation

Result	No. of Patients	No Evidence of Disease[a]	Alive With Recurrent Cancer
No residual cancer	17	13 (76)	0
Microscopic residual	11	4 (36)	2
Gross residual	34	8 (24)	3
Total	62	24 (40)	5

[a] Numbers in parentheses are percentages.

Survival

The entire group of 85 patients considered eligible for operation was evaluated in terms of survival. Currently, 26 patients are alive without evidence of recurrence, and 5 are alive with disease. Of the 85 patients, 62 had a thoracotomy. The reasons thoracotomy was not performed were treatment-related death (1), myocardial infarction during treatment (2), disease progression on treatment (7), and patient refusal (13). Of the 13 patients who refused operation, 1 is alive and free from disease at 55 months, 1 died of myocardial complications 11 months after initiation of therapy, and all others died of cancer. The 7 patients who had disease progression during therapy all died of carcinoma. Of the 62 patients having thoracotomy, 2 died of respiratory complications at 3 and 4 months after surgical resection.

The Kaplan-Meier survival estimate for the entire group of 85 patients initially eligible for operation is 40% at 3 years with a median survival of 663 days (Fig 2). There were 39 patients with squamous cell carcinoma and 46 patients with adenocarcinoma or large cell carcinoma. The Kaplan-Meier survival estimates comparing these two groups of histologies is seen in Figure 3. Although the median survival for the patients with squamous cell carcinoma is 30.3 months and the median survival for patients with adenocarcinoma or large cell carcinoma is 17.6 months, there is no significant difference in survival ($p = 0.17$). Survival estimates for the 56 patients receiving cisplatin and 5-FU reveal a median survival of 20.9 months. The pretreatment program including VP-16 consisted of 29 patients who have a current median survival

Table 6. Staging of 17 Patients With No Residual Cancer

Clinical Stage	No. of Patients	Method of Staging	No. of Patients
T3 N2	8	Mediastinoscopy	5
T2 N2	3	CT, nodes ≥ 2 cm	5
		Thoracotomy	1
T3 N0	5	Chest wall invasion	4
		CT, into mediastinum	1
T4 N0	1	Tracheal involvement	1

CT = computed tomography.

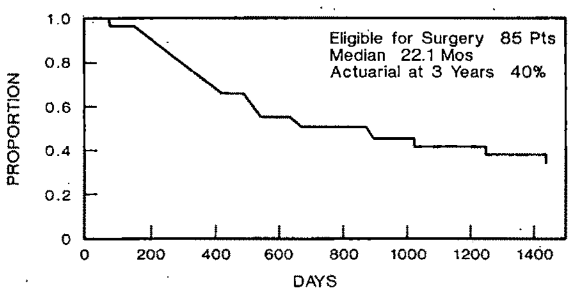

Fig 2. Kaplan-Meier survival estimate for the entire group of 85 patients initially eligible for operation.

of 34.2 months. However, follow-up is shorter, as the last patient entered this group in August 1987. There is no significant difference in survival between the two pretreatment groups ($p = 0.19$) (Fig 4). The survival estimate of the 62 patients undergoing thoracotomy is shown in Figure 5; median survival is 36.6 months.

Comment

The rationale for these phase II studies was founded on previous clinical reports that demonstrated a 36% to 56% response rate in patients with NSCLC limited to the chest with cisplatin-based chemotherapeutic regimens [8–11]. Longeval and Klastersky [9] reported on 107 patients treated with cisplatin and VP-16 who were not candidates for curative resection. The overall response rate was 38% (36/94) with 4 patients having complete remission. It was noted that in patients with local regional disease who had not received any prior therapy, the response rate was 56% (19/34) with three complete remissions. The median duration of response was 44 weeks, which was significantly longer than that in patients with disseminated disease. The authors suggested that this regimen of chemotherapy should be evaluated in a trial with either operation or irradiation. These collective results suggest that cisplatin-containing regimens produce response rates of approximately 50% in patients who have stage III NSCLC.

Takita and colleagues [12] published encouraging preliminary results from a trial in which a cisplatin-containing combination chemotherapy program was administered before radiation therapy or operation in patients with locally advanced NSCLC. There were 128 patients placed on various chemotherapeutic regimens, and 24 originally considered to have inoperable disease underwent resection after chemotherapy. There were 2 operative deaths and 2 early deaths from causes other than tumor; all postmortem examinations revealed no evidence of residual tumor. Of the remaining 20 patients, 15 were alive 4 to 27 months after pulmonary resection, and 5 were alive with evidence of disease 4 to 27 months postoperatively.

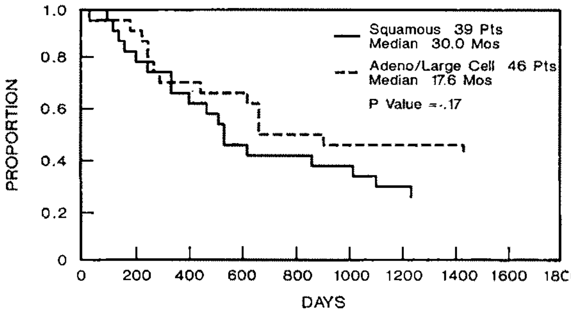

Fig 3. Kaplan-Meier survival estimates comparing patients with squamous cell carcinoma and those with adenocarcinoma or large cell carcinoma. The difference is not significant.

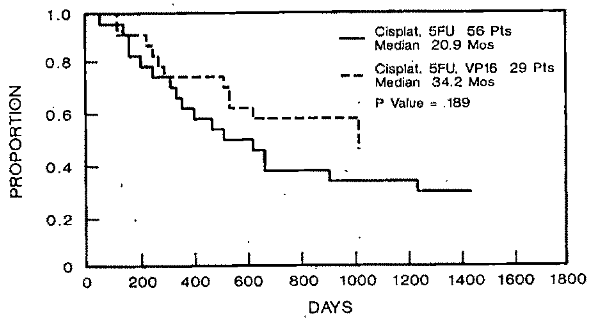

Fig 4. Kaplan-Meier survival estimates for the two pretreatment groups. The difference is not significant. (Cisplat = *cisplatin;* 5FU = *5-fluorouracil;* VP16 = *etoposide.)*

Preoperative irradiation was proved not to be effective in a prospective and randomized multicenter clinical trial [13]. However, more modern radiation sources and staging techniques may improve these results. Kirschner [14] used mediastinoscopy to define 48 clinical stage III patients for preoperative irradiation and resection. He achieved an impressive resectability rate of 95.7% (45/47), and the 5-year disease-free survival rate by the life-table method was 20% with a median survival of 24 months. Perez and co-workers [15] reported a prospective randomized study comparing various radiation doses and schedules in the treatment of 365 patients with inoperable NSCLC. The 1-year survival was 50% and the 2-year survival, 25%. These findings indicate that renewed consideration of preoperative therapy as a treatment program for clinically advanced NSCLC is indicated.

Raut and associates [16] utilized a pretreatment program of cisplatin, bleomycin sulfate, and mitomycin C in the treatment of patients with nonresectable squamous cell lung cancer. There were 32 patients entered into the

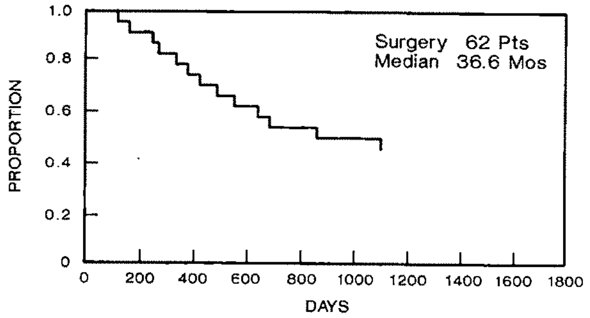

Fig 5. Kaplan-Meier survival estimate for the 62 patients undergoing thoracotomy.

program, and resection was accomplished in 29. Three (10.3%) had no tumor cells in the resected specimen, and 4 (13.8%) had only microscopic residual. It was thought that resectability was enhanced by this pretreatment program.

The overall results in these two phase II trials of combination preoperative chemotherapy and irradiation support the feasibility of this program. Leukopenia developed in 1 patient who died of sepsis. This was the only treatment-related death among the 85 patients considered eligible for operation. Two myocardial infarctions caused death during treatment, and a possible relationship between 5-FU and myocardial injury has been reported [17]. Nausea and vomiting was severe in 15 of the 85 patients, and drug doses were modified in these instances. Four cycles of chemotherapy and irradiation were completed in 94% (80/85) of the patients. The refusal of 13 patients to have operation after completing four cycles of therapy suggests that the pretreatment program is difficult to endure. However, 6 of these patients did accept an additional two cycles of therapy when they refused operative intervention.

Between March 1963 and January 1972, a total of 175 patients with bronchogenic carcinoma received preoperative irradiation. Although they were not clinically staged, they are a somewhat similar group of patients. The resection rate for this group was 91%. The resectability rate in the group of patients reported here was 97% (60/62), which indicates that this preoperative treatment program can improve resectability. The operation is difficult, as there is frequently marked fibrosis around the hilum and fascial and vascular planes are usually obliterated. There were four bronchial fistulas after resection, three after pneumonectomy and one after right middle and lower lobectomy. It is recommended that care be taken to preserve bronchial arteries, but this is frequently difficult when a radical resection is required. Pneumonectomy stumps should be covered with pedicled flaps of muscle, mediastinal fat, or pleura in an attempt to minimize fistula occurrence. Postoperative atelectasis requires vigorous supportive therapy with repetitive fiberoptic bronchoscopic aspiration. Tracheostomy may be required to clear secretions and maintain an adequate airway.

A complete resection was achieved in all but 2 patients. This finding is important because, at present, complete resection remains the most effective form of therapy for NSCLC. The results based on the histological findings at operation indicate that the pathological response is an important prognostic factor in long-term survival (see Table 5). Of the 17 patients who had no residual cancer in the resected lung tissue or regional lymph nodes, 76% (13/17) are alive and free from disease. There was 1 operative death, and only 3 patients have died of recurrent cancer. Two died of metastasis to the brain, and 1 had diffuse distant metastatic disease. There are no patients who had local recurrent carcinoma, and this finding further emphasizes the fact that histological sterilization of the tumor is a favorable prognostic finding. Of the 11 patients who had microscopic residual disease, 36% (4/11) are alive and free from disease. Recurrent carcinoma has occurred locally in 2 patients, and 5 patients have distant metastatic disease. In this group, brain metastasis has developed in only 1 patient. Of the 34 patients with gross residual carcinoma, 24% (8/34) are alive and free from disease. The recurrences in this group have been distant metastasis only in 7, brain only in 6, local only in 5, local and distant in 3, and brain and other sites in 1. For the entire group of 62 patients who underwent thoracotomy, local recurrence only has occurred in 7 patients.

Table 7. Comparison of Clinical Assessment of Response Based on Chest Roentgenograms and Pathological Examination of Specimens After Surgical Resection

	Pathological Response			
Clinical Response	No Visible Tumor	Microscopic Residual	Gross Residual	Total
Complete	0	3	1	4
Partial	15	8	24	47
None	2	2	7	11

In some patients, there were major discrepancies between clinical response and pathological findings. It is, therefore, not possible to speculate regarding the appropriateness of a surgical resection. On two occasions, residual large bulky disease turned out to be only necrosis and fibrosis, and no residual cancer was identified. Similar bulky disease contained only microscopic residual cancer in 2 other patients. In contrast, 4 patients with normal-appearing chest roentgenograms after four cycles of therapy had residual gross or microscopic cancer (Table 7). Surgical resection should always be included in any therapeutic program of this type, as clinical response is an unreliable predictor of the subsequent course of the patient. This point is further substantiated by the fact that of the 13 patients who refused operation, only 1 remains alive and free from disease.

The protocol for this study was designed to include all stage III patients. There were 18 patients who were staged T3 N0 without clinical evidence of positive mediastinal lymph node invasion. There were 9 who had invasion of the chest wall, 6 with computed tomographic evidence of mediastinal invasion, and 3 who had cancers less than 2 cm from the carina in the right mainstem bronchus. The survival in this group of patients is 9 without evidence of disease and 4 alive with disease; 5 have died of the disease. The T3 N0 group of patients have generally done better, and this finding indicates that if patients with clinical stage T3 N0 NSCLC are to be included in future prospective randomized trials, the study should be stratified for T3 N0 and N2 disease.

The status of the 5 patients who are alive with disease suggests that an aggressive approach to solitary metastasis should be considered. A solitary brain metastasis developed in 2 patients, both of whom have had resection. They are alive 24 and 48 months after craniotomy and irradiation to the brain. A solitary adrenal metastasis developed 24 months after resection in another patient, and this was removed with a current survival of 6 months after adrenalectomy. Two other patients alive with disease have metastatic carcinoma in the contralateral lung and mediastinum after pneumonectomy.

There is currently no significant difference in survival between patients with adenocarcinoma or large cell carcinoma and those with squamous cell carcinoma. There is also no significant difference in survival when the two different chemotherapeutic drug programs are compared. The tumor was sterilized in 14% (8/56) of the patients in the two-drug program and in 31% (9/29) of those in the three-drug program. This may indicate that added drugs are of benefit. The patients who have undergone operation have a more favorable outcome, with a median survival of 36.6 months.

Our overall result of a survival estimate of 40% at 3 years in the 85 patients eligible for operation compares favorably with the results in other studies. Hilaris and associates [18] reported on 53 patients with operable stage III NSCLC who had all gross disease removed surgically and, after resection, were treated by brachytherapy and external irradiation. The 5-year actuarial survival was 30%. Mountain [19] discussed 497 patients who were clinically staged as having N2 disease. Estimated survival at 5 years was 4.9% with a median survival of 11 months. Of this group, 168 patients underwent surgical resection, and survival was improved to an estimated 5-year rate of 28.8% with a median survival of 22 months. Sherman and co-workers [20] described 53 patients with advanced localized lung cancer who were treated by preoperative irradiation followed by operation in 46. The 5-year actuarial survival was 18%. Resectability was 83% (38/46), and operative mortality was 4% (2/46).

The recent report of Martini and associates [21] on the effects of preoperative chemotherapy in patients with N2 M0 NSCLC is encouraging and supports further investigational studies. Our protocol has acceptable toxicity, complete resection is accomplished in the majority of patients, and survival estimates are encouraging. We hope to achieve better results in patients with clinically advanced bronchogenic carcinoma by this and similar neoadjuvant therapies, and will continue to explore improved methods of treatment.

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DISCUSSION

DR JACK A. ROTH (Houston, TX): Administration of systemic therapy preoperatively in patients with lung cancer is a theoretically attractive concept. The tumor size can be reduced, facilitating a complete resection. Micrometastases can be treated when the cell number is minimal and when the tumor cells are less likely to develop resistant clones. However, these theoretical advantages have yet to be convincingly translated into improved patient survival. Appropriately controlled clinical trials in which this approach has been extensively investigated have not demonstrated improved survival for patients with head and neck or esophageal cancers. Several groups have reported on preoperative chemotherapy or combined chemotherapy and radiation therapy in lung cancer, and Dr Faber has now updated one of the largest series.

Reports in the literature indicate that patients with completely resected stage III cancer have a median survival of 12 months. Dr Faber and associates report a 22-month median survival for patients treated with combination chemotherapy and irradiation preoperatively. Although these results appear promising, historical comparisons can be unreliable. Stage III is heterogenous and includes patients with N2 disease as well as those with chest wall invasion and negative lymph nodes. More stringent selection of patients with better performance status could result in an apparent improvement in survival compared with historical series.

The data analysis demonstrates the dwindling denominator phenomenon. Survival of patients undergoing operation is computed using a denominator that is reduced by the patients who die or who are removed during the course of the study. However, no exclusions occur in the historical control series, and therefore survival is apparently improved. Patients dying of chemotherapy-related causes and those refusing operation should be included in the survival statistics. The overall survival that Dr Faber gave of 22 months is, therefore, the best estimate of efficacy.

Definition of eligibility criteria is one of the most difficult problems in the design of studies for stage III patients. Not all patients in this study had histological confirmation of N2 disease. The postoperative stage is not reliable because it may be altered by preoperative therapy. Dr Faber, how many of your patients who survived more than 2 years were in the favorable T3 N0 group?

A number of questions remain unanswered. What is the best chemotherapy combination? Cisplatin appears to be an essential component, but all the combinations used to date have similar response rates. The complete response rate of 27%, described in the manuscript, is modest, especially considering that irradiation was also given with the chemotherapy. Is radiation therapy essential? It may contribute to toxicity, but may not contribute to efficacy.

I congratulate Dr Faber and his colleagues on their fine results.

DR MICHAEL BURT (New York, NY): The Memorial Sloan-Kettering experience with preoperative chemotherapy in patients with NSCLC was presented to this Society 1 year ago [21]. In our initial feasibility study, 41 patients with clinically apparent stage IIIA (N2) disease were treated with cisplatin plus mitomycin and vinblastine sulfate preoperatively with a 73% major response rate and a 75% resectability rate in responders. No radiation therapy was given before operation. We have now entered 68 patients in this study, and the response rate to chemotherapy and the resectability rate have remained essentially unchanged. We believe that chemotherapy given preoperatively to patients with locally advanced lung cancer can produce sufficient tumor reduction to allow a complete resection in the majority of patients. Perhaps this will translate into improved survival.

Two questions need answers. Is combining irradiation with chemotherapy necessary? Can we identify specific subsets of patients with stage III disease who would most benefit by neoadjuvant therapy?

DR THOMAS W. SHIELDS (Chicago, IL): I will simply emphasize what Dr Roth had to say. You really cannot take a small number of patients with T3 disease and place them in a study with patients with N2 disease. If a study like this is to be done, its author must be critical of how the patient group is established because different subgroups influence the overt results differently. I think that we have to be a little bit more specific as to how we classify and how we judge the results when the group of patients is as diverse as the one reported.

Another aspect of which I think we should be a little critical is the fact that these are very small numbers. Doctor Faber was quite critical of the small numbers that were presented earlier in the meeting.

I will also remind you of some ancient history, as I am one of the older gentlemen in the crowd. In the Veterans Administration series of preoperative irradiation, 26% of the tumors were sterilized. These were all biopsy-proven tumors initially. This had absolutely no effect whatsoever on the outcome.

Despite my criticisms, I think this is a very important study. However, I believe we must be a little more critical in the selection of patients to be evaluated.

DR FABER: I agree with Dr Roth that in future neoadjuvant trials involving patients with NSCLC, proper stratification of T3 N0 patients must be made. However, I am not certain that the T3 N0 patient should be eliminated from these trials. Reported survival in this group of patients remains at approximately 35%, and if we could improve on this figure, preoperative therapy would certainly be worthwhile. In our group of 26 patients who are currently alive and free from any evidence of cancer at present, there are 9 patients who were staged T3 N0. Of these 9, 3 had chest wall invasion without any evidence of mediastinal adenopathy, 4 had obliteration of mediastinal fascial planes as defined by the computed tomographic scan, and 2 had cancer within 2 cm of the carina. The original plan of the study was to use this protocol of neoadjuvant therapy for stage III patients, and that is why T3 N0 patients were included.

The evaluation of sites of failure revealed that 17 of 43 patients who died of cancer had local failure, and the remaining 26 died of distant disease.

I can only estimate how many of the patients received a full dose of chemotherapy, and that figure should approximate 90%. Treatment doses are modified for patients who have had severe nausea and vomiting and could not tolerate the full dose. Five patients did not receive all four cycles of preoperative therapy because of severe radiation esophagitis in 3 and severe nausea and vomiting in 1. However, 80 of the 85 patients entered into the study did receive four cycles of therapy, and I believe this indicates that this is a tolerable regimen.

Dr Burt asked whether it is necessary to add radiation therapy to chemotherapy in this type of treatment program. This phase II study was designed to achieve the best result possible, and those familiar with the literature on this subject know that cisplatin and irradiation together are synergistic in their action. We were attempting to achieve as complete a response as possible and also to perform a complete resection in as many patients as possible;

our resection rate was 97%. In designing this study, we postulated that irradiation combined with chemotherapy would provide the patient a better opportunity for long-term survival.

Dr Shields is correct in stating that larger groups of patients are needed to achieve statistical significance. That is why we are suggesting and attempting to show that this program of neoadjuvant therapy is feasible. The data have been presented so that cooperative groups can consider this type of therapy for future phase III trials. However, while we await future phase III trials, we will continue to modify our neoadjuvant phase II trials in an attempt to improve survival in patients who have clinically advanced lung cancer.

Important Notice From The Society of Thoracic Surgeons

Annual Meeting Changes

After extensive deliberation, the Council voted unanimously to return the time of the annual meeting to the January–February period beginning in 1991. The following dates and places have been selected by the Council.

25th Annual Meeting
September 11–13, 1989
Baltimore, Maryland

Interim Meeting
September 22–23, 1990
Chicago, Illinois

26th Annual Meeting
February 18–20, 1991
San Francisco, California

The interim meeting of September 22–23, 1990, will resemble that of the very successful interim meeting held in Dallas, Texas, January 30–February 1, 1987. Many members have requested that this format be repeated. In addition to its scientific component, this meeting will emphasize the socioeconomic aspects of cardiothoracic surgical practice, issues that currently require extensive time and effort by the Council and committees of The Society. The 26th Annual Meeting in February 1991 will have the usual annual meeting format.

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Automated Control of Postoperative Hypertension: A Prospective, Randomized Multicenter Study

Delos M. Cosgrove III, MD, John H. Petre, PhD, John L. Waller, MD,
Jonathan V. Roth, MD, Carol Shepherd, RN, and Lawrence H. Cohn, MD

Departments of Thoracic and Cardiovascular Surgery and Cardiothoracic Anesthesia, The Cleveland Clinic Foundation, Cleveland, Ohio; Department of Anesthesia, Emory Clinic, Atlanta, Georgia; and Division of Cardiothoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts

Hypertension after a cardiac operation is a frequent phenomenon. Complications resulting from this include bleeding, disruption of vascular suture lines, subendocardial ischemia, and possible cerebrovascular accidents. Treatment with sodium nitroprusside has become accepted practice to prevent these complications. To improve control of arterial blood pressure, a closed-loop system for sodium nitroprusside administration was developed. A prospective, randomized multicenter study was carried out postoperatively in 180 cardiac surgical patients to evaluate the performance of this system compared with manual control of infusion. Adherence of mean arterial blood pressure to ±10% of the target blood pressure occurred 85% of the time with the automatic system and 61% of the time with manual regulation ($p < 0.0001$). With the automatic system, there was less hypertension (9% versus 22%; $p < 0.0001$) and hypotension (6% versus 22%; $p < 0.0001$). The superior control of hypertension was achieved more rapidly with less requirement for nurse regulation of infusion rate. The superior control of blood pressure resulted in less chest tube drainage in the automatic mode (720 mL versus 840 mL; $p < 0.05$).

(Ann Thorac Surg 1989;47:678–83)

Hypertension after a cardiac operation is a well-recognized and described phenomenon. The incidence of hypertension varies with cardiac pathology, operative procedure, and definition of hypertension. After valve replacement, the reported incidence ranges between 8% and 12% [1]. After myocardial revascularization, a higher incidence, ranging from 17% to 73%, is found [2–4]. Complications resulting from postoperative hypertension include bleeding, disruption of vascular suture lines, subendocardial ischemia, and possible cerebrovascular accidents. Because this morbidity and mortality are theoretically avoidable, treatment of hypertension has become accepted practice.

Postoperative hypertension is relatively brief in nature, lasting several hours. Sodium nitroprusside is the drug most commonly administered to control transient hypertension because it decreases systemic vascular resistance and has a rapid onset and short duration of action. To avoid complications, rapid and consistent control of hypertension is essential. The quickly changing hemodynamics in a patient after a surgical procedure demand frequent adjustments of the nitroprusside infusion rate to maintain desired mean arterial blood pressure. This requires a substantial amount of time and effort on the part of the nurses [5].

To improve regulation of arterial blood pressure when using sodium nitroprusside, several authors [6–14] have proposed the use of an automated closed-loop system to obtain better control of hypertension, avoid extremes of hypotension and hypertension, and reduce the demands on the time of the intensive care nurses.

Stimulated by the pioneering efforts of Sheppard [7] and Slate [8], The Cleveland Clinic initiated an independent effort in 1979, which resulted in a clinically useful and reliable closed-loop system for the administration of sodium nitroprusside [15]. In 1982, a joint venture was begun with the IVAC Corporation, which resulted in additional modifications and improvement in the performance of the control system. This system was demonstrated effective in animals [9]. To evaluate the clinical efficacy, safety, and usefulness of the resultant system, a randomized prospective study was carried out at The Cleveland Clinic, Emory University, and Brigham and Women's Hospital. The patient study compared the results of the automated system with those obtained manually by trained, experienced intensive care nurses.

Material and Methods

The IVAC Titrator model 10K closed-loop sodium nitroprusside system is a dedicated microprocessor-based instrument that controls the infusion rate of a standard IVAC variable-pressure volumetric pump, model 560i, connected by an interface cable. The Titrator 10K uses two separate algorithms: the first is active during the process of lowering the patient's mean blood pressure to a desired level (transient control mode); the second is an enhanced proportional, integral, and derivative algorithm designed to maintain the mean pressure at a desired level (linear control mode).

Presented at the Twenty-fourth Annual Meeting of The Society of Thoracic Surgeons, New Orleans, LA, Sep 26–28, 1988.

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0003-4975/89/$3.50

Table 1. Surgical Procedures

Procedure	Automatic Mode (n = 90)	Manual Mode (n = 90)
Myocardial revascularization	66	75
Aortic valve replacement	9	5
Repeat myocardial revascularization	6	3
Mitral valve replacement	4	2
Other	5	5

The system "learns" from the patient's response to nitroprusside, and uses "learned information" in calculating subsequent infusion rate adjustments. The arterial blood pressure is sensed every 1⁄100 of a second. The infusion rate is adjusted every 10 seconds. Should blood pressure drop rapidly, an aggressive infusion rate reduction program prevents overdosing of the patient, often reducing the infusion rate even when mean arterial pressure is greater than the target pressure. The Titrator can be placed in manual mode, thus reverting control of the model 560i pump to the operator through the front panel switches as though the Titrator were not present.

A magnetic tape recording device (Memodyne) was connected to the system and documented, on a real-time basis for all study patients, incoming transducer signal, infusion pump variables, and Titrator functions, such as the control mode (automatic or manual). The Memodyne device is a data-recording tool used for research purposes only; it was not an integral part of the IVAC closed-loop regulator system.

The protocol was reviewed by the respective institutional human investigation review boards, and informed consent was obtained. One hundred eighty patients were prospectively assigned in a random fashion according to the odd-even status of the hospital number to have the administration of nitroprusside regulated manually or in the automatic mode. There were 90 patients in each of the two study groups. The average age was 59.3 ± 9.6 years (± the standard error of the mean) in the automatic mode group and 65.2 ± 9.2 years in the manual mode group. In the automatic mode group, 84.4% of the patients were male and in the manual mode group, 78.9%. The surgical procedures performed are listed in Table 1. Blood pressures were recorded by the Memodyne recorder at 10-second intervals. There were 216,210 determinations in the automatic mode group and 228,726 determinations in the manual mode group. The investigation logged 600 total hours of recorded data in the automatic mode and 635 hours under manual control.

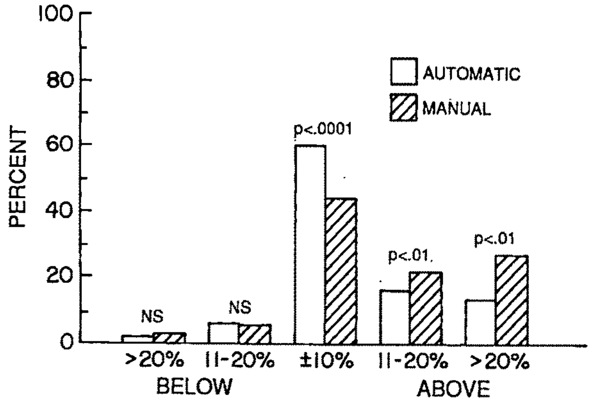

Fig 1. Distribution of blood pressure determinations for the first ten minutes.

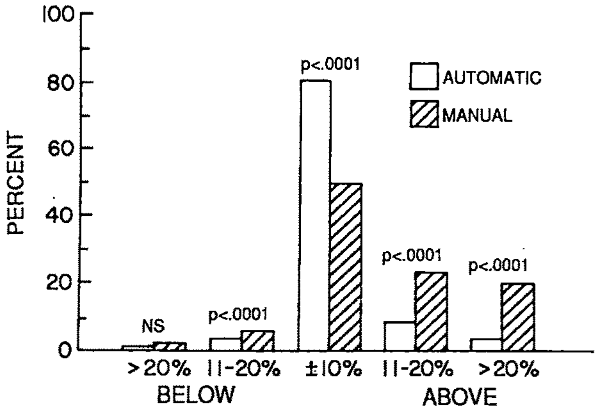

Fig 2. Distribution of blood pressure determinations for the second ten minutes.

An analysis compared the two methods at various time intervals and demonstrated the range of the resultant mean pressure relative to the desired mean blood pressure. Blood pressures were grouped in five categories: more than 20% less than the desired mean; 11% to 20% less than the desired mean; within ±10% of the desired mean; 11% to 20% greater than the desired mean; and more than 20% greater than the desired mean.

Chest tube drainage was recorded from the time of operation until 7:00 AM the following morning.

Each patient was analyzed individually for each time frame. The time frames were divided into six windows of 0 to 10 minutes, 10 to 20 minutes, 20 to 30 minutes, 30 to 45 minutes, 45 to 60 minutes, and remaining time. A mean percent error ([actual − desired]/desired × 100) was calculated for each patient for each time interval. These values were then compared for the two groups (automatic mode and manual mode) with Student's t test. A p value of 0.01 or less was considered significant.

Results

Because of the potential for large oscillations in blood pressure at the beginning of treatment with nitroprusside, the first three 10-minute intervals were analyzed separately. Automatic control was superior to manual control in regulating hypertension. More pressures remained within the desired blood pressure range while avoiding the extremes of hypotension and hypertension (Figs 1–3). During this period, there was a dramatic improvement in the control of blood pressure between the first two periods in the automatic mode with little change in the manual mode.

To evaluate the ability of the automatic system to

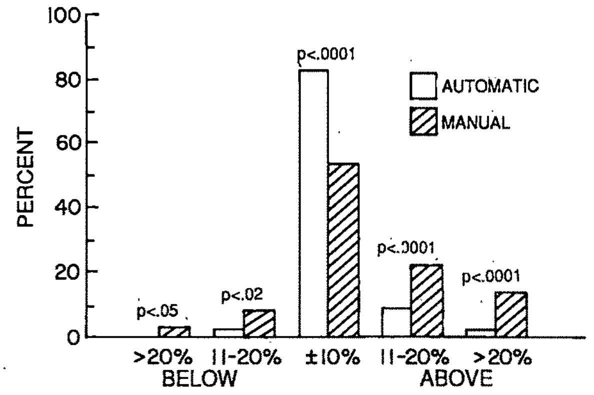

Fig 3. Distribution of blood pressure determinations for the third ten minutes.

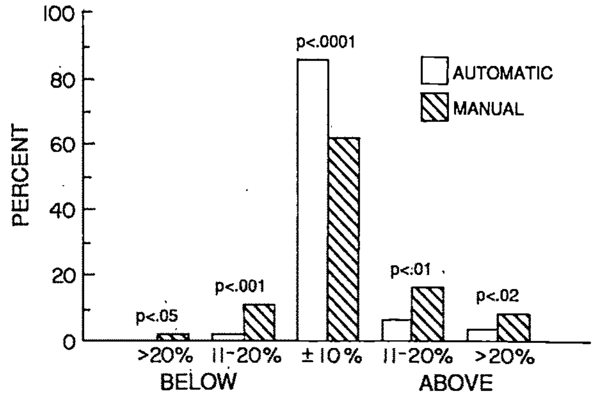

Fig 5. Distribution of blood pressure determinations from 45 to 60 minutes.

control blood pressure during a period when the requirements for nitroprusside were stable, the next two 15-minute periods were separately analyzed. A significantly greater percentage of blood pressure determinations fell within ±10% of the desired mean with the automatic system during these two periods. Analysis also demonstrated less hypotension and hypertension in the automatic mode group (Figs 4, 5).

To evaluate the period when requirements for nitroprusside were decreased and the infusion rate was tapered, the remaining time intervals were analyzed. The desired range for mean arterial blood pressure was obtained a higher percentage of the time with the automatic system than with the manual system, and hypertension and hypotension were less common (Fig 6).

When all blood pressure determinations for the entire study were analyzed, a significantly greater percentage of determinations fell within the ±10% range for the automatic system, with substantially fewer determinations of hypertension and hypotension (Fig 7).

To further evaluate the ability of the two techniques to achieve regulation at a desired mean arterial blood pressure, the mean percent error from the target blood pressure of the entire group was calculated. The mean percent error for the automatic mode group was lower than that for the manual mode group ($p < 0.0001$) (Fig 8).

The data were analyzed at individual study sites to determine the influence caused by a divergent patient population, intensive care personnel, and surgical and anesthesia practices. For the overall time period, the mean percent error (the percentage of deviation from the desired blood pressure) ranged from 4.9% to 5.8% for the automatic mode group and 10.1% to 10.9% for the manual mode group (Fig 9). The automatic control system had nearly identical results at each institution and produced significantly superior regulation of the mean arterial blood pressure.

To evaluate the rapidity by which hypertension was controlled by each of the two methods, mean percent error from the desired blood pressure was evaluated at various time intervals. During the first ten minutes of control, performance of the automated system was better than that of the manual system. The mean percent error was stabilized to less than 10% within the first ten minutes. This level of control was not achieved until after 45 minutes in the manual control mode (Fig 10).

When the automated mode was used, there was a significant reduction in the amount of time nurses spent to adjust the infusion rate of nitroprusside. In the automated mode, a mean of 0.45 change per hour was experienced by the nursing staff, whereas 6.03 changes per hour occurred in the manual mode ($p < 0.0001$).

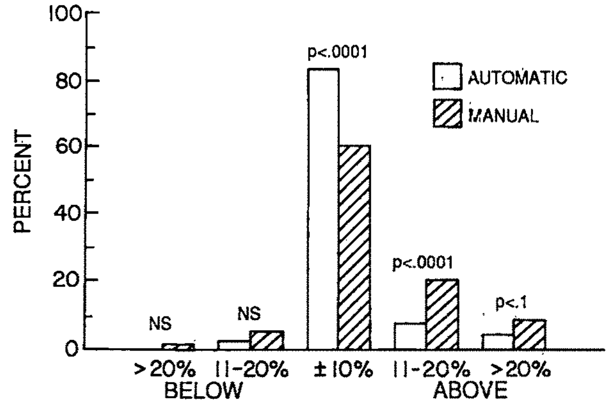

Fig 4. Distribution of blood pressure determinations from 30 to 45 minutes.

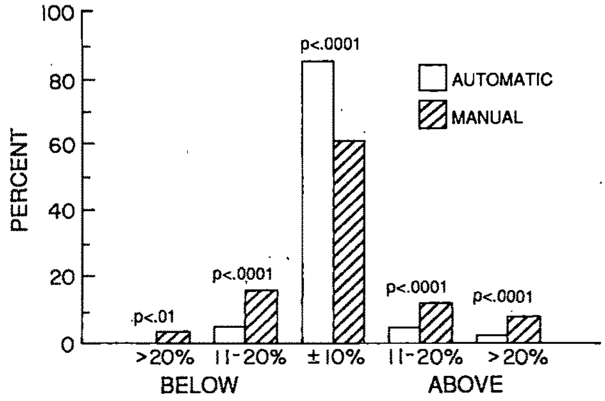

Fig 6. Distribution of blood pressure determinations for the remainder of the time.

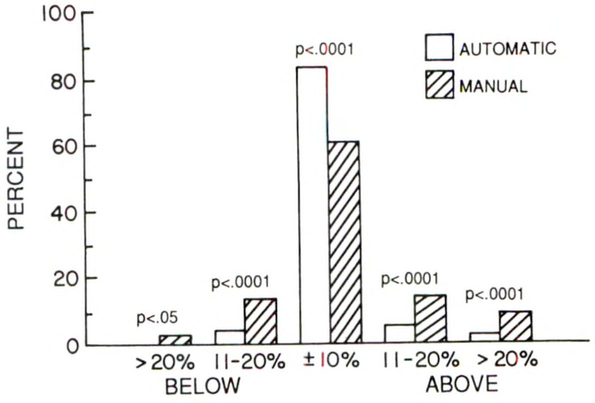

Fig 7. Distribution of blood pressure determinations for the entire study period.

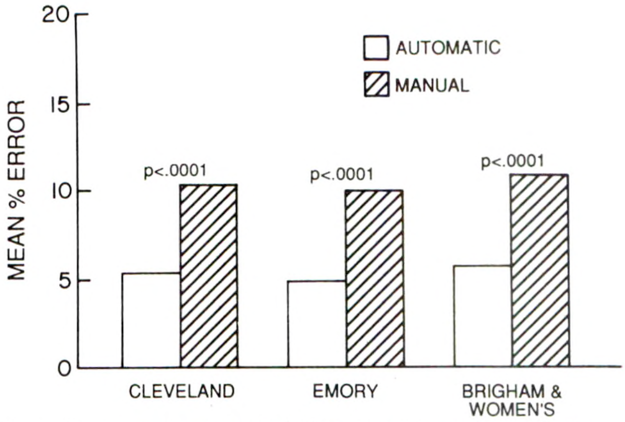

Fig 9. The automatic system had a lower mean percent error from desired blood pressure at all three study sites.

Chest tube drainage was less in patients under automatic control (720 ± 312 mL) compared with those controlled in the manual mode (840 ± 462 mL) ($p < 0.05$).

Comment

The study of cardiac surgical patients after operation to evaluate an automated closed-loop system that controls the infusion of nitroprusside is appropriate for several reasons. First, hypertension is common in this setting, thus allowing controlled studies. Second, the hemodynamics are extremely labile, providing a rigorous test for any system. Finally, the complications associated with hypertension, such as blood loss, are measurable, resulting in an end point that can be measured.

The superiority of the automatic system for administering nitroprusside is evident in this study. Adherence to within ±10% of a target blood pressure was superior at all time intervals measured for the automatic system. Similarly, control of hypertension was dramatically better at all time intervals. In the entire study, 20% of the blood pressure determinations in the manual control mode were more than 10% greater than target pressure compared with 6% for the automatic system ($p < 0.0001$). Hypotension was equally well eliminated by the automatic system. Patients in the manual mode group had 22% of their determinations more than 10% less than the target pressure whereas only 9% of the automatic mode group were in this range ($p < 0.0001$). The evidence that blood pressure control is superior in the automatic mode is unequivocal.

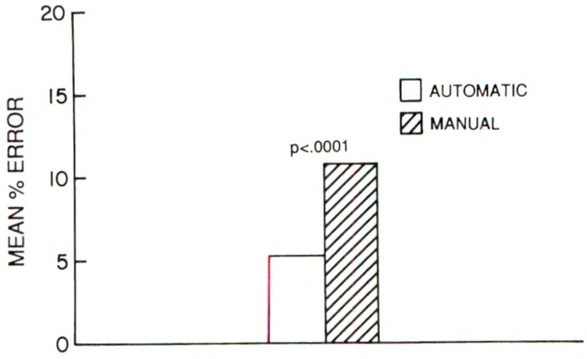

Fig 8. The mean percent error from desired blood pressure for the automatic mode group was less than that for the manual mode group.

To be optimally effective and to minimize complications, control of hypertension must be rapid. The automatic system demonstrated this characteristic by reducing the mean percent error to less than 10% in the first ten minutes. This same degree of control required 45 minutes for patients with nurse-controlled infusions. Rapid response in the automatic mode is a direct result of specifically written algorithms that have a transient control mode.

Several features of this device enhance patient safety during the administration of nitroprusside. To avoid the dangerous complication of hypotension, the algorithm is designed in such a way that should the blood pressure begin to drop rapidly, an aggressive infusion rate reduction program rapidly reduces the infusion rate. This

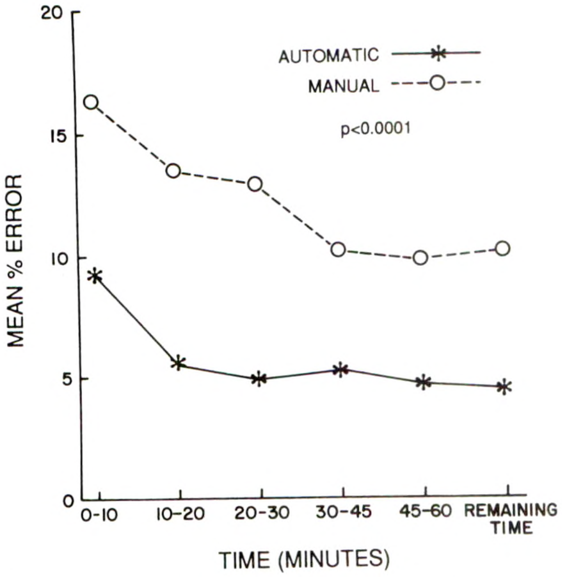

Fig 10. Hypertension was more rapidly controlled with the automatic system, which reduced the mean percent error to less than 10% in the first ten minutes.

capability prevents overdosing of the patient even in instances where the mean arterial blood pressure is greater than desired. To avoid nitroprusside toxicity, infusion rate limits of 299 mL/h and 10 μg/kg/min and a total dose of 4 mg/kg of nitroprusside administered are included in the design. Other safety features include an automatic internal system for systematic checks during power-up and routine use, and an infusion shutoff when the mean arterial pressure signal is severely deranged for two minutes or if an internal component fault is detected. Further safety features include circuitry that rejects artifacts, such as motion of the pressure tubing and loss of signal because of blood sampling. This maintains the previously determined infusion rate and prevents inappropriate infusion rate adjustment during such activities.

The differences between institutions in patient population, intensive care personnel, and surgical and anesthesia practices provided test environments to determine the capability of the automated system to control blood pressure under diverse circumstances. The versatility of the system was demonstrated by the almost identical performance at all three institutions. This performance bodes well for the wide application of this technology.

It is well recognized that a substantial percentage of the time and attention of intensive care nurses is required to tightly control the blood pressure of a patient receiving an infusion of nitroprusside. One study [5] demonstrated that 40% of patients undergoing a cardiac surgical procedure received nitroprusside postoperatively and that 16% of nursing time was spent regulating the infusion of this drug. The effectiveness of this study demonstrates that infusion rate manipulation by nurses can be reduced 15-fold. This device has the potential of allowing nursing personnel to spend more time on other patient-related activities.

With an increased interest in reducing homologous blood transfusions to minimize the risk of acquired immunodeficiency syndrome and hepatitis, a major benefit of the Titrator system may be the potential for reducing postoperative chest tube drainage. The observed reduction of chest tube drainage and bleeding indirectly provided by the automated system appears to offer a major opportunity to reduce blood transfusions. The potential to further reduce chest tube drainage by controlling blood pressure at lower than usual levels has yet to be investigated. This system provides the opportunity to attempt this in a highly controlled and safe fashion.

Although this device was developed solely for use in adults after cardiac operations, its use in hypotensive anesthesia has been explored [9]. Neurosurgery, hypertensive crisis, aortic surgery, and cardiopulmonary bypass are logical areas of potential application in the future.

Cardiac surgery has directly benefited very little from the advancements associated with computer technology and artificial intelligence. This infusion control system represents a unique application of advanced technology to solve a specific clinical problem. It is envisioned that as additional sensors and algorithms are developed, closed-loop systems for controlling serum glucose, calcium, blood volume, cardiac output, oxygen saturation, cardiopulmonary bypass, ventilators, and anesthesia machines will become clinical realities that will increase the safety of cardiac operations. This system represents the development of a new drug-delivery system, but it is only the first step in the utilization of automated control technology, which holds vast potential.

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DISCUSSION

DR FRANCIS ROBICSEK (Charlotte, NC): I thank The Society for asking me to review this paper, and I congratulate Delos Cosgrove and his associates on their very well constructed and carefully executed study, and at the same time, give proper credit to the technical developer.

The question one should ask after the presentation is not why, what, and how, but probably why so late? In the early 1970s, following John Kirklin's footsteps, we "closed the loop" and introduced automated infusion and transfusion in eight intensive care beds at our department. It is hard to forget that when we first approached computer engineers with our plans, their initial respect turned first into amazement and then into amusement over our clinical methods, which were certainly primitive compared with industrial sophistication. When we inquired whether they could measure urine output and chest tube drainage electronically, and together with left atrial pressure use them as an algorithm for volume replacement, one of them burst out laughing and said, "Doc, this machine can send this cup of urine to the moon, measure it there, and bring it back to run your 'drip, drip, drip' machine."

In 1988, it is an anachronism that while we trust our life to an autopilot to fly us to New Orleans, we let our patient's blood pressure rise and fall like a roller coaster because a nurse, among the multiplicity of his or her chores and exhaustible attention span, is simply unable to keep track of it.

I have only a few questions. First, do you believe that the application of this technique will allow you to decrease the nurse/patient ratio in your intensive care unit? We were hoping this would occur, but in our practice, it never materialized.

Second, the classic indication for nitroprusside infusion is not hypertension but elevated circulatory resistance. Do you intend to make your system more sophisticated to include automatic feed-in of cardiac output and calculation of resistance?

Finally, I am somewhat surprised that after you were so successful in keeping the blood pressure down, you are not turning your program "in reverse" and using it to administer vasopressors (in the case of hypotension) or dopamine hydrochloride based on automatic cardiac output measurements. Do you plan to do this?

Again, I compliment Dr Cosgrove and associates for bringing the technique of intravenous drug therapy closer to the modern age.

DR KENNETH M. TAYLOR (London, England): I also compliment Dr Cosgrove and his co-workers for this important study. At the Hammersmith Hospital, we have had the opportunity to study the IVAC Titrator system, and we have used it in a prospective study of our cardiac surgical patients.

Almost 100,000 data points were collected, and the superiority of control of blood pressure was essentially identical to that presented by Dr Cosgrove's group. The automatic mode achieved target blood pressures during the study period in 90% of patients, whereas the manual mode group with our experienced intensive care nurses was at around 45%. We found consistently that the nurses tended to err on the side of allowing the pressure to be slightly on the high side of the target range, and there is no significant difference in the low incidence of hypotensive episodes described.

Like Dr Cosgrove's group, we found that the time necessary to get the blood pressure into the target range was on the order of 20 minutes in the automatic mode compared with more than two hours for the patients being controlled manually.

We were particularly impressed with some of the safety features built into the algorithm of this nitroprusside infusion system. For example, in 1 patient, the target level of blood pressure had been achieved well but at the expense, if you like, of a consistently rising infusion rate for nitroprusside. Administration of a bolus of intravenous vasodilators by the surgical staff resulted in a fall in the blood pressure. When this sequence of events occurs, the algorithm of the system will shut off the Nipride (sodium nitroprusside) infusion totally if the blood pressure falls to less than 75% of the target level.

The interesting thing is that if such a patient were being managed manually by the intensive care nurse, the nurse is unlikely to restart the Nipride infusion until the blood pressure returns to target levels. The ability of this system to sense rates of change and adjust appropriately means that it switches the Nipride infusion back on again while the blood pressure is still low but climbing, and achieves restoration of the target control levels much more quickly than might be anticipated with manual control. Our experience with the Titrator system in Hammersmith, therefore, is entirely in accord with the data presented by Dr Cosgrove and his group.

What was the response of the nursing staff in the various institutions in your study, Dr Cosgrove? We found that after some initial and I think inevitable skepticism, the nursing staff was thoroughly convinced of the efficacy and value of the Titrator system, particularly in the management of difficult patients. We also believe that this is an important first step in the application of computer technology to data collection and to patient management after routine cardiac procedures.

DR COSGROVE: Dr Taylor alluded to nursing staff acceptance of this device. We noted that the nurses were initially cautious in their acceptance, but by the time they had worked with it for approximately 2 weeks, they found it preferable to manual titration.

We also hoped that we would be able to reduce the nurse/patient ratio, but found that this is not possible. We think that we are going to be able to maintain our current nurse/patient ratio as nurses do increasingly complex work, for example, running patients on left ventricular assist devices and caring for much more acutely ill patients.

Dr Robicsek asked if we have not directed our nitroprusside therapy at the wrong end point. Should we be controlling systemic vascular resistance as opposed to controlling blood pressure? It became clear to us that we needed to have continuous on-line cardiac output to derive systemic vascular resistance and, in fact, titrate nitroprusside to achieve the optimal systemic vascular resistance. Currently, this project is well underway and promises to bear fruit in the next few years.

Finally, I caution people not to proceed directly to the use of vasopressors based solely on hypotension in this sort of closed-loop device. The reason that we give vasopressors and all cardiotonic drugs is not just to raise blood pressure but, more importantly, to increase cardiac output. Until such time as we have an on-line sensor device to continuously measure cardiac output, I do not think it is reasonable to expect that we can use dopamine, dobutamine hydrochloride, or Levophed (norepinephrine bitartrate) in a closed-loop system.

Cardiac surgery has not benefited directly from the advances associated with computer technology and artificial intelligence. This infusion control system represents a unique application of advanced technology to solve a specific clinical problem. It is envisioned that as additional sensors and algorithms are developed, closed-loop systems for controlling serum glucose, calcium, blood volume, cardiac output, oxygen saturation, cardiopulmonary bypass, ventilators, and anesthesia machines will become clinical realities that will increase the safety of cardiac operations.

This device represents the development of a new drug-administration system, but it is only the first step in the utilization of automated control technology, which holds vast potential.

Coronary Sinus Versus Aortic Root Perfusion With Blood Cardioplegia in Elective Myocardial Revascularization

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The role of retrograde coronary sinus cardioplegia in patients undergoing elective coronary artery bypass grafting has not been fully defined. Forty patients undergoing coronary artery bypass grafting received either aortic root (20 patients) or coronary sinus (20 patients) cold potassium blood cardioplegia. The patients were similar with respect to age, ventricular function, severity of coronary artery disease, cross-clamp time, completeness of revascularization, frequency of internal mammary artery grafting, and mean infusate volume and temperature. The time required to deliver the initial dose of cardioplegic solution and the time to achieve arrest were prolonged in the coronary sinus group ($p < 0.001$ and $p < 0.02$, respectively). There were no differences between the two groups postoperatively with regard to enzymatic indices, hemodynamic measurement, or clinical outcome. Right ventricular function was preserved equally in both groups. We conclude that coronary sinus cardioplegia is a safe alternative to aortic root perfusion, but offers no advantage in elective myocardial revascularization.

(Ann Thorac Surg 1989;47:684–8)

Retrograde coronary sinus perfusion has recently reemerged as an attractive alternative for the delivery of cardioplegia. Experimental and clinical studies have documented its ability to achieve adequate preservation during global myocardial ischemia. Despite this evidence, the retrograde technique has not gained widespread use. Compared with aortic root cardioplegia (ARC) delivery, coronary sinus infusion can be associated with a delay in cardiac arrest, cumbersome infusion techniques, and the potential for inadequate right ventricular preservation. It is unclear which route of cardioplegia delivery is more advantageous clinically. The present study was undertaken to evaluate the efficacy of retrograde coronary sinus cardioplegia (RCSC) compared with standard ARC in patients undergoing elective myocardial revascularization.

Material and Methods

Between January 1988 and May 1988, 40 patients undergoing elective coronary artery bypass grafting alternatively received cold blood cardioplegia either through the aortic root (ARC group, 20 patients) or through the coronary sinus (RCSC group, 20 patients). The protocol was approved by the institutional review board at St. Louis University Group Hospitals on September 26, 1988 (IRB No. 5287).

Data recorded included age, sex, history of a transmural myocardial infarction, number of vessels bypassed, and frequency of internal mammary artery grafting. Regional wall motion abnormality was measured by left ventricular score as defined by The Coronary Artery Surgery Study [1]; left ventricular function was assessed also using left ventricular end-diastolic pressure. Major coronary artery stenosis was defined as occlusion of 50% or more of the left main trunk and 70% or more for all other coronary arteries in at least one view.

Anesthesia management included endotracheal intubation and maintenance with fentanyl (20 to 50 μg/kg), pancuronium bromide (0.1 mg/kg), and enflurane. Patients were ventilated with 100% oxygen. Catheters were placed in the radial artery, and a balloon-tip catheter was positioned in the pulmonary artery (Opticath P7110; Oxymetric, Inc, Mountain View, CA) for hemodynamic measurements. Cardiopulmonary bypass was established using ascending aortic and bicaval cannulation employing moderate systemic hypothermia (30°C nasopharyngeal temperature) and hemodilution (20% to 25% hematocrit). The extracorporeal circuit contained a membrane oxygenator (SciMed model I-3500-2A; SciMed Life Systems, Inc, Minneapolis, MN) primed with 1,800 mL of crystalloid and 500 mL of 5% albumin. In patients with retrograde infusion, the coronary sinus was cannulated through a short right atriotomy.

The composition of the infusate and the delivery were identical in both groups except for the route of delivery. Cardioplegia consisted of 4:1 dilution of blood with 0.9% normal saline solution, which contained 20 mEq/L of sodium bicarbonate. The initial dose was 10 mL/kg and

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Table 1. Summary of Patient Data[a]

Variable	ARC Group	RCSC Group	*P* Value
Age (yr)	66.4 ± 1.7	68.1 ± 1.7	NS
Age range (yr)	53–77	54–79	NS
Sex (male)	11	17	NS
Left ventricular score	6.9 ± 0.8	8.8 ± 0.77	NS
No. diseased vessels	2.9 ± 0.07	2.9 ± 0.01	NS
Left main	3	8	NS
No. vessels bypassed	3.9 ± 0.23	3.6 ± 0.3	NS
Internal mammary artery	13	13	NS
Duration of CPB (min)	128 ± 5.6	130 ± 4.3	NS
Cross-clamp time (min)	76 ± 4.9	78 ± 6.1	NS

[a] Where applicable, data are shown as the mean ± the standard deviation.

ARC = aortic root cardioplegia; CPB = cardiopulmonary bypass; NS = not significant; RCSC = retrograde coronary sinus cardioplegia.

contained 14 mEq/L of KCl. Reinfusion (5 mL/kg) was performed at 20-minute intervals but contained only 6 mEq/L of KCl. The ARC patients received cardioplegia exclusively through the aortic root using a DLP catheter (DLP model 23009; DLP, Walker, MI) at an infusion pressure of 80 to 100 mm Hg. The RCSC patients received cardioplegia exclusively through the coronary sinus using a DLP balloon-tip retrograde coronary sinus infusion catheter (DLP model 940-15) inserted through a small right atriotomy. Infusion pressure was maintained at 35 to 40 mm Hg.

Topical myocardial cooling with lactated Ringer's slush and a cardiac insulation pad for phrenic nerve protection were employed in all patients. A left ventricular vent was not used. Distal anastomoses were constructed with aortic cross-clamping; proximal anastomoses were performed without global myocardial ischemia. The volume and temperature of the cardioplegic solution and the time required for infusion were recorded as were the interval to achieve cardiac arrest and the ventricular septal temperature (Shiley myocardial temperature probe DPM; Shiley Inc, Irvine, CA).

Operative variables recorded included cardiopulmonary bypass and cross-clamp times, the number of trials necessary to separate the patient from the extracorporeal circuit, and the number of electric shocks required to achieve ventricular defibrillation.

Blood samples for assessment of lactate dehydrogenase isoenzymes 1 and 2 (LDH_1 and LDH_2) were obtained on postoperative days 1 and 2. A ratio between LDH_1 and LDH_2 that was 1.0 or greater was considered indicative of myocardial injury. Measurements of the myocardial-specific isoenzymes of creatine kinase were obtained before aortic cross-clamping and at 1, 2, 3, 4, 8, 12, and 24 hours after unclamping. A myocardial fraction higher than 50 U/L was considered diagnostic of myocardial injury.

Hemodynamic measurements were obtained at 0.5, 1, 2, 3, 4, 8, 12, and 24 hours after cross-clamp removal. Measurements recorded included systemic, right atrial, pulmonary artery, and pulmonary capillary wedge pressures and cardiac output (thermodilution technique). Using standard formulas, values for cardiac index and right ventricular and left ventricular stroke work indices were calculated at identical intervals [2, 3].

Data were analyzed using the Statview 512$^+$ statistical software package (Brainpower, Inc, Calabasas, CA). Univariate analysis of discrete variables was performed using χ^2 analysis or Fisher's exact test where appropriate. Student's *t* test was employed for continuous variables. A *p* value of 0.05 or less was considered significant. Mean values are expressed as plus or minus the standard deviation.

Results

The preoperative and intraoperative patient data are shown in Table 1. There were no differences between groups with respect to age, left ventricular function, severity of coronary artery disease, completeness of revascularization, frequency of internal mammary artery grafting, duration of extracorporeal circulation, or cross-clamp time.

The temperature of the infusate was approximately 5°C in all patients, and the mean ventricular septal temperature achieved was not different between the groups (ARC, 10.7° ± 0.5°C, and RCSC, 11.0° ± 0.7°C; p = not significant [NS]). Although a greater volume of cardioplegic solution was used in the ARC group, the difference was not significant (1,767 ± 117 versus 1,688 ± 119 mL; p = NS). The time required to infuse the initial dose of cardioplegic solution and the interval to achieve complete electrocardiographic arrest were significantly longer in patients in whom the retrograde route was used (Figs 1, 2). In no patient did electromechanical activity return during the interval between cardioplegia infusions.

No patient required intraaortic balloon counterpulsation, and there were no operative deaths. The need for inotropic agents after termination of cardiopulmonary bypass was more frequent in the retrograde group, but the difference was not significant (6 versus 2; p = NS). The

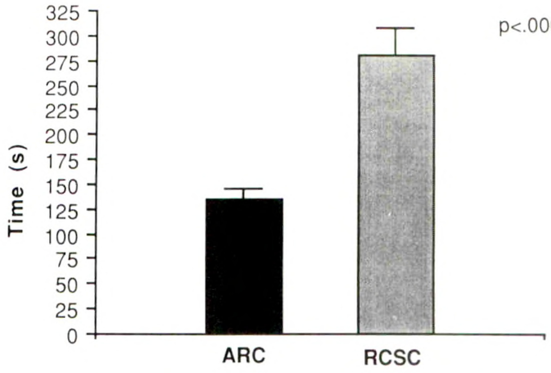

Fig 1. Comparison of infusion time for the initial dose of cardioplegic solution. Data are shown as the mean ± the standard error of the mean. (ARC = *aortic root cardioplegia;* RCSC = *retrograde coronary sinus cardioplegia.*)

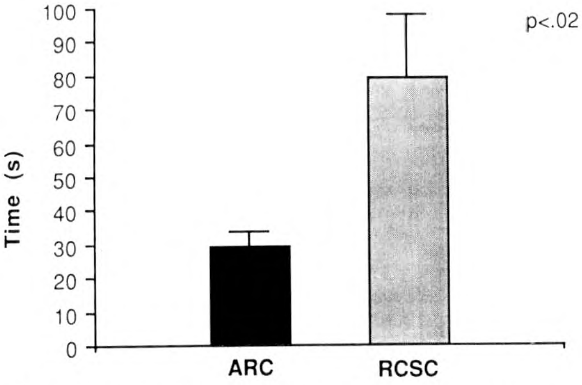

Fig 2. Comparison of the time to achieve electromechanical arrest during the initial cardioplegia infusion. Data are shown as the mean ± the standard error of the mean. (ARC = *aortic root cardioplegia;* RCSC = *retrograde coronary sinus cardioplegia.)*

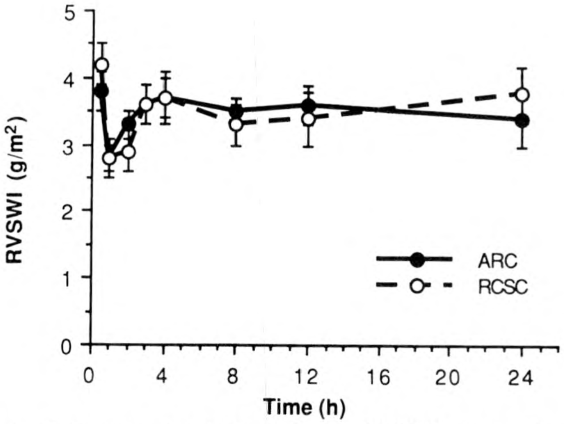

Fig 4. Right ventricular stroke work index (RVSWI) *at intervals after cross-clamp removal. Data are shown as the mean ± the standard error of the mean.* (ARC = *aortic root cardioplegia;* RCSC = *retrograde coronary sinus cardioplegia.)*

number of trials required to separate the patient from the extracorporeal circuit (ARC group, 1.0 ± 0.09, and RCSC group, 1.1 ± 0.08; p = NS) and the number of electric shocks required to defibrillate the heart (ARC group, 2.2 ± 0.3, and RCSC group, 1.9 ± 0.4; p = NS) were also similar. The frequency of new-onset postoperative atrial fibrillation was slightly greater in patients receiving ARC (31% versus 20%; p = NS). No significant differences were noted between the ARC and RCSC groups with respect to the ratio of LDH_1 and LDH_2 levels measured on the first and second postoperative days. Four patients had perioperative transmural infarctions as defined by new Q waves on the electrocardiogram and elevated myocardial enzymes (ARC group, 3, and RCSC group, 1). The curve of the myocardial-specific isoenzyme of creatine kinase demonstrated peak enzyme levels at four hours (ARC group) and eight hours (RCSC group) after aortic unclamping (Fig 3). Although a trend toward greater enzyme release was noted in those patients receiving retrograde cardioplegia, the difference was not significant.

Right ventricular performance was well preserved by either route of cardioplegia delivery (Fig 4). There was a trend toward better left ventricular function in those patients receiving anterograde cardioplegia but the difference reached significance only at 12 hours after aortic unclamping (Fig 5). It was no longer different at 24 hours, when both groups reached baseline levels.

Comment

Cardioplegia delivery through the aortic root is an established method for safe and effective myocardial preservation during elective revascularization. Cardioplegia administration is simple, diastolic arrest is rapid, and ventricular function after reperfusion is well preserved. In patients with coronary artery disease, the major disadvantage of this technique is the potential heterogeneous distribution of the cardioplegic solution because of coronary artery stenoses or occlusions. Areas supplied by obstructed coronary arteries can be subject to inadequate cardioplegia delivery, which can cause insufficient cooling of the myocardium and also allow continued electrome-

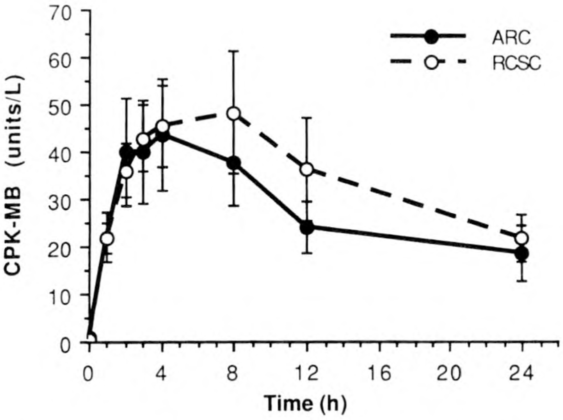

Fig 3. Comparison of myocardial enzyme release: levels of the myocardial-specific isoenzyme of creatine kinase (CPK-MB) *obtained from venous blood samples before and after aortic cross-clamping. Data are shown as the mean ± the standard error of the mean.* (ARC = *aortic root cardioplegia;* RCSC = *retrograde coronary sinus cardioplegia.)*

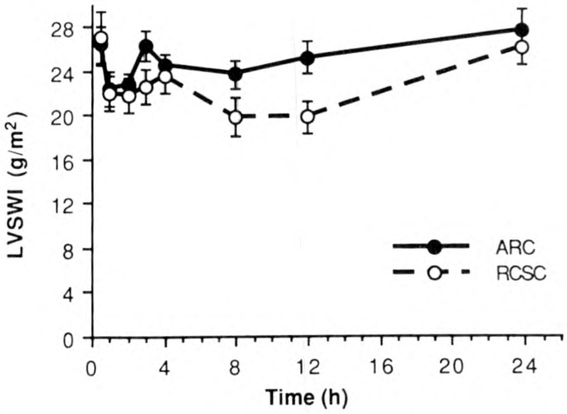

Fig 5. Left ventricular stroke work index (LVSWI) *at intervals after cross-clamp removal. Data are shown as the mean ± the standard error of the mean.* (ARC = *aortic root cardioplegia;* RCSC = *retrograde coronary sinus cardioplegia.)*

chanical activity. These phenomena result in poor myocardial preservation and increased risk of clinically detectable myocardial injury in the perioperative period. In addition, this route of cardioplegia delivery may be less attractive in patients who have some degree of aortic insufficiency in addition to the coronary artery disease.

Retrograde coronary sinus perfusion, on the other hand, relies on the nonobstructed coronary venous system for its delivery, and this provides a homogeneous distribution of cardioplegia to the myocardium. In addition, this route of delivery is effective regardless of the competence of the aortic valve.

A number of investigators [4–6] have determined experimentally that retrograde perfusion of cardioplegia is safe and possibly a more effective means of myocardial protection than aortic root delivery, particularly in the setting of acute coronary artery occlusion. Despite these experimental results, there is a paucity of comparative clinical data demonstrating superior regional or global myocardial protection with retrograde cardioplegia [7]. This present study directly compares both routes of cardioplegia delivery in a prospective fashion to assess the adequacy of myocardial preservation.

The principal advantage of coronary sinus cardioplegia should be better regional myocardial perfusion beyond totally obstructed coronary arteries. Using temperature mapping by thermographic analysis, Shapira and associates [8] found more uniform cooling in inflow-restricted regions of patients undergoing operation for severe and extensive coronary artery disease when retrograde cardioplegia was used. In our series, ventricular septal but not regional temperature was monitored. When combined with topical myocardial cooling, both routes of cardioplegia delivery provided similar reduction in septal temperature. It is important to recognize that in the setting of elective revascularization, patients usually have chronic stable angina patterns. Thus they have coronary collaterals that are sufficiently well developed to ensure homogeneous myocardial cooling independent of the route chosen for cardioplegia infusion.

A number of drawbacks have been associated with retrograde perfusion techniques. Overinflation of the balloon catheter or high intracoronary sinus infusion pressure can cause rupture of the coronary sinus. This did not occur in our series. Coronary sinus injury has been reduced with the introduction of the soft, pear-shaped balloon catheter designed by Gundry [9]. The perfusion pressure can be monitored and maintained between 35 and 40 mm Hg, thus avoiding myocardial hemorrhage and edema, which can result from barotrauma during retrograde infusion. Although a pursestring suture in the coronary sinus has been suggested for catheter stabilization, we have not found this advantageous. Several investigators [10, 11] have advocated the concomitant use of an aortic root vent to permit the coronary artery effluent to escape, thus maintaining a coronary sinus–aortic pressure gradient. We did not routinely find this necessary, as the majority of coronary sinus flow empties into the cardiac chambers through the anterior cardiac veins and the lesser coronary venous system.

A major objection to retrograde perfusion has been inadequate right atrial and right ventricular protection. It has been suggested that the right ventricle might be underperfused by the retrograde method because the right ventricular free wall drains directly into the thebesian veins and the right atrium. Experience in this study demonstrates good preservation of right ventricular stroke work index postoperatively, and supports the previous observations of Menasché and associates [12] that coronary sinus perfusion can adequately preserve right atrial and right ventricular function.

The need for bicaval cannulation and slow administration of cardioplegic solution have made surgeons reticent to adopt the retrograde method. This study demonstrated that the time to infuse the initial dose of cardioplegia and the time to achieve electromechanical arrest were significantly prolonged when the retrograde route was used. The heart is fibrillating during this prolonged initial infusion interval, and this may cause a reduction in high-energy metabolites and late ventricular dysfunction. This could explain the trend toward improved left ventricular stroke work index in patients receiving anterograde cardioplegia. Buckberg [13] recently suggested that this problem can be circumvented by infusing cardioplegia first through the aortic root to achieve early diastolic arrest and subsequently through the coronary sinus or right atrium to provide more homogeneous distribution. We did not combine these techniques to avoid a potential bias in assessing the advantages of one method over the other.

Reasoning that the additional thebesian flow from the right side of the heart may be helpful, some authors [14, 15] have preferred right atrial cardioplegia over coronary sinus infusions. Fabiani and colleagues [16] demonstrated superior left ventricular function, lower cardiac isoenzyme levels, and fewer postoperative arrhythmias when the right atrial route was used for delivery instead of the coronary sinus. More recently, Diehl and associates [17] combined aortic root and right atrial cardioplegia delivery in patients undergoing elective myocardial revascularization. They demonstrated better postischemic right ventricular recovery and a slight improvement in left ventricular ejection fraction in patients receiving combined cardioplegia delivery compared with conventional aortic root infusion. The advantages of right atrial cardioplegia delivery appear to be simplicity of technique and contact cooling of all right-sided structures. The presence of a patent foramen ovale or an atrial septal defect precludes the use of this technique.

Our study was intentionally limited to the subset of patients with adequate left ventricular function and a stable pattern of angina pectoris. In this select patient population, we have demonstrated that myocardial preservation using the coronary sinus is equivalent to conventional aortic root cardioplegia but offers no advantage.

However, the clinical profile of the patient having coronary artery bypass grafting is rapidly changing. Increasing numbers of revascularization procedures are being performed urgently on patients with ongoing myocardial ischemia. It is this subset of patients with an ischemic myocardium who might be better served with the retrograde cardioplegia technique. Patients with unstable angina pectoris, those who require reoperation in the presence of stenotic bypass grafts, and patients with acute ischemia after failed balloon angioplasty all have lesions that preclude optimal delivery of cardioplegia by the anterograde route. Retrograde cardioplegia may prove to be a more effective technique for myocardial preservation in these emergency situations.

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Spontaneous Rupture of the Esophagus: A 30-Year Experience

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This retrospective review of 34 patients with spontaneous rupture of the esophagus, which spans a 30-year period, attempts to identify areas in diagnosis and therapy that might alter the dismal prognosis. The diagnosis and definitive surgical repair of Boerhaave's syndrome were frequently delayed. Delay resulted in a significant increase in complication rates. Pain (85%) and vomiting (71%) were the only common historical events suggesting the diagnosis. Physical examination was of aid in the diagnosis in only the 9 patients (27%) who demonstrated cervical or mediastinal emphysema. The initial chest roentgenogram was abnormal in 97% of the patients, but was interpreted as "compatible with perforation of the esophagus" in only 27%. Esophagography was diagnostic in 23 of 24 patients in whom it was used. Thoracentesis was of little diagnostic aid, but pleural fluid pH was measured in only 15% of the patients. Prompt surgical repair, regardless of time after onset, appears to be the indicated therapy.

(Ann Thorac Surg 1989;47:689–92)

Since Boerhaave's original dramatic description in 1724 of esophageal rupture in Lord High Admiral (Baron) Wessenaer, this lesion has frequently resulted in catastrophe. It is seldom seen [1], is commonly misdiagnosed, and is associated with a high mortality and almost universal morbidity [2]. This retrospective review of 34 patients with spontaneous esophageal rupture seen within a 30-year period at our hospitals is an attempt to identify areas in diagnosis and therapy that might alter the dismal prognosis. Only patients with true spontaneous rupture are included; excluded are all patients with iatrogenic, foreign body, or external perforations as well as those with preexisting esophageal disease.

The usually described "classic" history is that of a previously healthy person who vomits strenuously and experiences immediate onset of epigastric or substernal pain, or both, with collapse, shock, and, when untreated, early death. These classic symptoms are frequently absent, a factor that contributes to the common delay or error in diagnosis. The site of rupture is usually immediately supradiaphragmatic in location and usually on the left. Factors believed to contribute to rupture include a very high intraesophageal pressure created by strenuous vomiting or retching, a lack of esophageal serosa leading to structural weakness of this portion of the esophagus, and a high pressure gradient across the esophageal wall resulting from the surrounding negative intrathoracic pressure.

Material and Methods

Between July 1, 1958, and September 1, 1988, the diagnosis of spontaneous rupture of the esophagus was confirmed in 34 patients. Twenty-seven (79%) were men, and age ranged from 23 to 88 years with a median age of 53 years. All patients were followed until discharge from the hospital or death; survivors were followed as outpatients until early complications had resolved.

Data are presented as simple numbers, percentages, and frequency distributions. Significance of the differences in discrete variables was evaluated with contingency tables using χ^2 analysis where indicated. Differences in complications between groups were analyzed by Fisher's exact two-tailed t test using SPSS (Statistical Package for the Social Sciences) on the University of Tennessee DEC VAX 8600 series mainframe.

History and Physical Examination

The most common presenting complaint was rapid onset of pain (29 patients or 85%) or vomiting (24 or 71%), or both. A relationship between onset of symptoms and recent eating was noted in 11 patients, and the specific lack of such a correlation was noted in 9 (45%) of the 20 patients who answered this question. The pain was abdominal in 16 patients, thoracic in 9, and located in the shoulder in 4. Pain occurred before or without nausea and vomiting in 8 patients. Twenty-four patients reported vomiting to be a major part of their early symptomatology, 5 of whom vomited gross blood. Recent ingestion of a large quantity of alcohol was reported by only 7 of the 25 patients in whom this relationship was noted.

Physical examination was of little diagnostic aid. The completeness of the documentation of physical examination was poor in this retrospective study, as these patients were admitted under emergency conditions and the written physical examination findings were, all too often, sketchy. Four patients were in frank shock, 3 others had a high fever, and 2 were cyanotic on admission. Crepitation in the neck or chest was present in 9 patients (27%) on admission and developed in 6 others within three days.

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Diagnosis and Management

Routine chest roentgenographic examinations were interpreted as "normal" in 1 patient, as "compatible with perforation of the esophagus" in 9, and as revealing nondiagnostic abnormalities in 24. More than half (18) of the patients demonstrated pleural effusion on roentgenographic examination: 11 (61%) on the left, 4 on the right, and 3 bilaterally. Mediastinal (with or without cervical) emphysema was noted in 9 patients (27%), nonspecific pulmonary infiltrations were present in 4, and intraperitoneal air was seen in 2. One patient had a widened mediastinum, which was interpreted as a thoracic aneurysm.

Esophagograms were not obtained in 10 patients; in 7, the diagnosis was considered obvious without the esophagogram, and in the other 3, diagnosis was delayed. Of the 24 patients who underwent esophagography, Gastrografin (diatrizoate meglumine and diatrizoate sodium solution) was used in 15, and contrast medium extravasated into the mediastinum or pleural space in all. In 9 patients, barium was used, with extravasation of contrast medium in 8. Thus, there was one false-negative esophagogram (4%).

Rigid esophagoscopy, done in 3 patients, was falsely negative in 2. Flexible esophagoscopy demonstrated the rupture in the single patient in whom it was done.

The admission diagnosis was correct in only 14 patients (41%). The most common incorrect diagnoses were perforated peptic ulcer (8 patients), acute pancreatitis (3), thoracic aneurysm (2), and pneumothorax (2).

Diagnostic thoracentesis was done in the 18 patients with obvious pleural effusion; in 13 of them, a simple pH measurement was omitted. The fluid obtained was usually described as "foul smelling," "old blood," or "dirty." Neither the gross appearance nor routine laboratory studies of the pleural fluid were of diagnostic value except in the 2 patients (of 5 in whom the pH was measured) with strongly acidic fluid.

All patients received multiple antibiotics intravenously. Nasogastric tubes were passed, and frequently another sump tube was placed in the upper esophagus to minimize further mediastinal contamination. Sterile saline solution with antibiotics (usually neomycin) was taken by mouth or was administered through a nasoesophageal tube for irrigation after thoracostomy tube drainage was established.

Primary surgical repair was carried out in 26 patients (Table 1). Interrupted nonabsorbable 4-0 sutures were used in 12 patients and were passed through the mucosa and submucosa. Separate muscle-layer closure was not usually possible because of extensive necrosis. In 14 patients, continuous absorbable 3-0 sutures were used. No discernible differences were noted in results between these patients and those with interrupted nonabsorbable sutures. Pleural flaps were used to cover the suture line in 20 patients.

Four patients had operation deferred from three days to 6 weeks after diagnosis because of poor clinical condition; 2 of them underwent repair, and 2 had Urschel exclusions. The 4 remaining patients, considered too critically ill for thoracotomy when the diagnosis was established, were treated by tube thoracostomy and various open drainage procedures with no attempt at esophageal repair.

Table 1. Surgical Procedures in 34 Patients

Procedure[a]	No. of Patients
Early	26
Thal patch	3
Exclusion	1
Late	4
Exclusion	2
None	4

[a] Early is defined as thoracotomy within 24 hours of diagnosis; late, as thoracotomy after 72 hours. None refers to patients who did not have thoracotomy, but had other surgical procedures.

The rupture was located in the left wall of the distal esophagus in 30 patients, and extended into the intraabdominal esophagus in 1 of them. The distal right wall was involved in 1 patient, and the midesophagus was the site in 3 patients.

During the last decade, intravenous hyperalimentation has been used after repair. Before then, gastrostomies, jejunostomies, and esophageal feeding tubes were used without a fixed protocol.

Results

Fourteen patients (41%) died including all 4 who did not have thoracotomy. Delay had no significant effect on mortality rate (33% in both groups).

Of the 20 survivors, 15 had major complications (Table 2); 9 had lung abscesses, extensive or long-standing pneumonia, or bronchopleural fistulas. Because contaminated or infective pleural effusion, transient fever, tachycardia, and atelectasis are considered part of the initial clinical picture of spontaneous rupture of the esophagus, these, when promptly resolved, were not considered major complications. No new complications appeared after discharge from the hospital, and there were no deaths related to the primary disease after discharge.

In contrast, the 14 patients who died exhibited 39 major complications: 6 had esophageal leaks; 11, major pulmonary problems; and 3, mediastinal abscesses.

Three patients underwent laparotomy before accurate diagnosis. Acute renal failure, sepsis, and multiple infections developed in all three. Two of the patients died.

Delay in diagnosis was defined as a time from onset of symptoms to establishment of the correct diagnosis exceeding 24 hours. Seventeen patients (50%) had such a delayed diagnosis. The delays resulted from both patient delay in seeking medical advice and incorrect initial diagnosis. Diagnostic delay (13 or 77%) was more common than patient delay.

Comments

Many of the published cases of Boerhaave's syndrome are included in articles on broader subjects, eg, iatrogenic

Table 2. Major Complications[a,b]

		Survivors[c] (n = 20)			
Complication	Nonsurvivors (n = 14)	Total	<24 h (n = 12)	>24 h (n = 8)	Total (n = 34)
Leaks	6 (43)	3 (15)	1 (8)	2 (25)	9
Pulmonary	11 (79)	9 (45)	3 (25)	6 (75)	20
Empyema	6 (43)	2 (10)	1 (8)	1 (13)	8
Acute renal failure	4 (29)	1 (5)	0	1 (13)	5
Cardiac	2 (14)	2 (10)	1 (8)	1 (13)	4
Mediastinal	3 (21)	1 (5)	0	1 (13)	4
Sepsis	2 (14)	1 (5)	0	1 (13)	3
Wound infection	2 (14)	1 (5)	0	1 (13)	3
Miscellaneous	3 (21)	1 (5)	1 (8)	0	4
Total	39	21	7[d]	14[d]	60
No./patient	2.8	1.1	0.6	1.8	

[a] Major complications exclude transient atelectasis, pneumonitis, tachycardia, empyema, and fever. [b] Numbers in parentheses are percentages. [c] Survivors are stratified into those who were diagnosed less than or later than 24 hours after onset of symptoms. [d] Significance: $p = 0.055$.

esophageal perforations and perforations due to a foreign body, carcinoma, caustic ingestion, Mallory-Weiss syndrome, or even an external missile [3–6]. This results in confusion in both diagnostic perception and therapeutic approach. The nonspecific findings on physical examination and chest roentgenographic examination probably also contribute to physician error.

The classic description was absent in most of our patients, and reliance on this clinical picture probably resulted in substantial error or delay in diagnosis. The rarer disorder (Boerhaave's syndrome) is not always considered initially in the differential diagnosis; more common diseases may be thought to be responsible for the symptom complex. When the diagnosis was strongly suspected and an esophagogram was made, the lesion was demonstrated in all but 1 patient. Esophagoscopy was not widely used; it was incorrect in 1 of the 3 patients in whom it was done and, for that reason, might impart a false sense of security when negative. It appears that only a heightened awareness of the disease and a suspicion about its presence, especially on the part of primary care physicians, can prevent delays or errors in diagnosis.

Delay in diagnosis did not affect mortality rates in our series. Delay of more than 24 hours is frequently reported to have a profound effect on the mortality [2–8]. However, these published series pertain to perforations of various causes, most commonly, iatrogenic. The review by Larsen and colleagues [2] of 1,787 patients from the world literature revealed a strong correlation between delay in treatment and mortality rate in iatrogenic perforations; their personal experience with Boerhaave's syndrome showed no effect on mortality rate between patients operated on in less than 24 hours (43%) and those operated on more than 24 hours (38%) after onset. Our patients having operation less than 24 hours after onset had a mortality rate of 33%; those diagnosed and operated on later than 24 hours after onset also had a mortality rate of 33%.

Delay in diagnosis appears to be the most important single factor leading to excessive complication rates. Table 2 correlates delayed diagnosis with complications. Patients with a delayed diagnosis who survived had an average of 1.8 major complications per patient, whereas those who died averaged 2.8 major complications per patient. Of those with prompt diagnosis and operation, 5 (42%) of 12 had no major complications, and the mean number of complications per patient was only 0.6.

Fisher's exact two-tailed t test on frequency of complications in these two groups (<24-hour and >24-hour delay) yielded a p value of 0.055. This rare disease has prevented statistical "proof" of most observations, but this p value is probably of clinical significance. The surgeons managing these patients have strong impressions that the severity as well as the frequency of complications was worse in the patients with a delay.

Presence of undigested food in pleural aspirates usually leads to the correct diagnosis. However, food is not usually recognized. Pleural fluid in patients with Boerhaave's syndrome has been observed repeatedly to be quite acid. Rupture through the esophageal wall into the left pleural space during violent vomiting allows acid gastric contents to gain direct entry into the pleural space. However, another mechanism may be responsible for the lesser, but progressive, degrees of acidity found in more subtle cases. Good and associates [9] demonstrated in rabbits that metabolism of white blood cells (polymorphonuclear leukocytes) present in response to inflammation causes an acidic fluid in the absence of gastric acid. Our experience and review of the literature suggest that the simple, but valuable, determination of pleural fluid pH is done all too infrequently.

Early primary repair offers the best chance of a smooth course and ultimate recovery. However, even under these more ideal circumstances, the mortality rate remains high. Our overall mortality of 41% compares with published ranges of 16% to 51% [2].

Nonoperative "conservative" therapy has been suggested in certain patients with esophageal perforations [10–12], especially when there are minimal symptoms, the extravasated area drains well back into the lumen of the esophagus, and there is no communication between the esophageal lumen and pleural space [10]. However, most of these successes have been in iatrogenic perforations diagnosed and treated early; experience with Boerhaave's syndrome is very limited.

The technique of esophageal repair is compromised frequently by the severe necrosis and inflammation found at operation. Although interrupted silk sutures are frequently recommended for repair, we (and others) prefer continuous absorbable sutures. A separate muscle layer cannot usually be developed because of the severe pathological processes. When feasible, however, the muscle is closed with interrupted absorbable suture. Our overall incidence of esophageal leak was 17% (5/30) of the patients having operation, 11% (3/28) among those in whom repair actually was done, and 15% (3/20) among survivors. These findings are comparable with or better than those in many published series.

It is important to cover the suture line with well-vascularized "healthy" tissue. When a thickened pleural flap is adequate, it is used. When the pleura is thin or attenuated, underlying intercostal muscle also is used. Richardson and co-workers [4] have developed techniques for and emphasized the use of muscle or diaphragmatic flaps.

Although prompt and accurate surgical repair, reinforced by pleural flaps or a Thal patch, is the definitive treatment, ancillary therapeutic techniques are important. These include broad-spectrum antibiotics in high doses at the first suspicion of mediastinitis, nasogastric decompression, sump drainage of the upper esophagus, antibiotic-containing fluids by mouth [13], and correction of fluid, electrolyte, and blood volume problems before, during, and after operation. In those patients in whom the diagnosis is delayed, complete drainage of the pleural cavities, nasogastric tube suction, and other supportive mechanisms, including hyperalimentation, are indicated.

When reviewing and comparing patients from a time span of several decades, the effects of changes in several factors can be important. From 1958 to the present, there have been major improvements in the general care of critically ill patients; these include parenteral hyperalimentation, more effective and specific antibiotics, use of computed tomographic scanning, widespread use of flexible endoscopes, safer anesthesia, better management of acute renal failure, and improvements in ventilators and respiratory care. However, when our results were analyzed by decades or by half-decades, there was no difference in survival rates as a function of time. Thus, there is no clear evidence that these improvements in armamentarium have had a significant effect on our mortality rates. Even though the true value of ancillary procedures could not be illustrated by comparing the patients from different time periods, we still believe them to be important.

Our limited experience indicates that diversion procedures are of questionable value and that late esophageal repair is more satisfactory. In cases of delayed treatment, we recommend surgical repair with the use of pleural or muscle flaps. In our report of 1958 [14], 1 patient had primary closure 49 days after rupture, and recovered. In the present series, successful outcome followed repair as late as nine days after diagnosis. These observations, as well as those of others [4, 13], seem to indicate that the decision not to close the esophagus because of the length of time after rupture probably is not wise.

These patients were managed in the affiliated hospitals of the University of Tennessee: Regional Medical Center, Baptist Memorial Hospital, Methodist Hospital (Central), and the Veteran's Administration Medical Center, Memphis. We acknowledge the clinical contributions of Drs Glenn Crosby, Rodney Wolf, and Charles Eastridge, as well as the many residents who participated in the care of these patients.

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Bronchoscopic Phototherapy at Comparable Dose Rates: Early Results

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Photodynamic therapy is a recently introduced treatment for surface malignancies. Since January 1987, 10 patients with endobronchial neoplasms have had bronchoscopic photodynamic therapy at similar dose rates (400 mW/cm) for total atelectasis (2), carinal narrowing with respiratory insufficiency (2), or partial obstruction without collapse (4). Two patients underwent photodynamic therapy as a preliminary to immunotherapy. Histologies included endobronchial metastases (colon, ovary, melanoma, and sarcoma, 1 each; and renal cell, 3) and primary lung cancer (3). The 2 patients with total atelectasis had complete reexpansion after photodynamic therapy, which permitted eventual sleeve lobectomy in 1. Carinal narrowing was ameliorated in the 2 patients seen with inspiratory stridor, thereby permitting hospital discharge. Endoscopically resected fragments after photodynamic therapy exhibited avascular necrosis. These data support further controlled studies of photodynamic therapy by thoracic surgical oncologists to define its limitations as well as to improve and expand its efficacy as a palliative or surgical adjuvant.

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Photodynamic therapy (PDT) has been the subject of reports concerning the management of endobronchial malignancies [1–4]. Photodynamic therapy uses the selective retention characteristics of dihematoporphyrin ether (DHE) in malignant tissue by activating cytotoxic mechanisms with exposure to visible light in the presence of oxygen. This approach theoretically spares nonmalignant tissue, which retains less DHE [5]. Amelioration of endobronchial obstruction as well as complete tumor response has been described by several institutions [1, 3]. Although these results are encouraging, inconsistencies in dose rate, input energy, and method of illumination have made these reports difficult to interpret from the standpoint of treatment efficacy and complication rates.

Since January 1987, we have investigated the use of bronchoscopic PDT for the management of endobronchial malignancies, chiefly by interstitial illumination at comparable dose rates and treatment energies. In performing this trial in this manner, our goal was to more accurately define the advantages, limitations, and complications of this therapy.

Material and Methods

Since January 1987, 10 patients under protocols of the National Cancer Institute have been considered eligible for treatment of endobronchial malignancy with PDT (Table 1). Seven patients were seen with a metastatic endobronchial neoplasm, and 3 had primary lung cancer. Eligibility criteria included total lung (2 patients) or lobar (2) collapse, progressive respiratory obstruction (3), asymptomatic endobronchial lesion (1 patient), and attempted airway management before treatment with immunotherapy protocols (2). No patient with purely extrinsic compression without an intrabronchial component was considered eligible for PDT, and the majority of patients (8) had multiple extrathoracic sites of metastatic involvement precluding direct surgical intervention via pulmonary resection. Seven patients had lesions in the main bronchus, carina, or bronchus intermedius. Only 5 of the 10 patients had disease that was purely intraluminal without an extrinsic component. The 5 patients with a combination of intrinsic and extrinsic disease had primary treatment of the intraluminal component via interstitial illumination of the tumor (see Laser Treatment Section).

Sensitizer

Dihematoporphyrin ether was provided by Photofrin Medical (Cheetowaga, NY; now Quadra Logic, Vancouver, BC, Canada) as a sterile solution, 2.5 mg/mL dissolved in 0.9% NaCl solution. Sixty-seven to 72 hours before laser irradiation, all patients received 2 mg/kg of DHE given intravenously over 15 minutes in 50 mL of 0.9% NaCl solution. After sensitizer administration, all patients were removed from direct exposure to sunlight.

Light Source, Light Delivery System, and Dosimetry

An argon pumped-dye laser (model PRT100; Coherent Inc, Palo Alto, CA) was used to generate 630-nm light with power levels up to 5 W. The 630-nm laser light was coupled into a fused silica fiber 600 μm in diameter (Quartz Products Corporation, Plainfield, NJ) to carry the light 54 m to the surgical suite. The treatment fiber, typically 400 μm in diameter, was coupled to the 600-μm fiber in the surgical suite. This permitted rapid inter-

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Table 1. Patient Characteristics and Results of Photodynamic Therapy

Patient No.	Age	Sex	Histology	Location	Intrinsic/ Extrinsic	Approximate Degree of Obstruction (%)		Distal Airway Visualization	Lobar Expansion	Recurrent Symptoms	Follow-up
						Before Therapy	After Therapy				
1	37	F	Colon	Left main	Intrinsic	100	20	Yes	Yes	No[a]	Alive, 18 mo
2	39	F	Ovary	Left main	Intrinsic	100	10	Yes	Yes	No	. . .
				Right main	Intrinsic	20	5	Yes	. . .	No	Dead, 315 days
3	60	M	Lung	Left main	Intrinsic	50	30	Yes	. . .	No[b]	. . .
				Right main	Both	90	40	Yes	. . .	No	Dead, 77 days
4	44	F	Melanoma	Left main	Both	100	100	Transient	Transient	Yes	Dead, 35 days
5	37	F	Lung	Apical segment, left upper	Intrinsic	100	10	Yes	. . .	No	Dead, 294 days
6	47	M	Renal cell	Left main	Both	100	60	Yes	. . .	Yes[b,c]	. . .
				Left main	Both	80	50	Yes	. . .	No	. . .
				Right main	Both	40	20	Yes	. . .	Yes	. . .
				Right main	Both	40	20	Yes	. . .	No	Dead, 111 days
7	40	M	Sarcoma	Bronchus intermedius	Both	100	100	No	No	Yes	Dead, 60 days
8	58	M	Lung	Right main	Intrinsic	80	0	Yes	. . .	No[a]	Alive, 98 days
9	44	F	Renal cell	Anterior segment, left upper	Both	100	10	Yes	. . .	No	Alive, 150 days
10	35	F	Renal cell	Posterior segment, left upper	Intrinsic	100	0	Yes	. . .	No	Alive, 120 days

[a] A sleeve lobectomy was performed after photodynamic therapy. [b] This patient had carinal disease. [c] Recurrent respiratory distress developed, and the patient underwent photodynamic therapy for the second time.

change of fibers during the procedure, and was necessary for evaluating fibers with differing tip light distribution or replacing fibers that became damaged.

The light distribution from a fiber was calibrated before treatment by measuring the power delivered into the surgical suite through a normal perpendicularly cleaved 400-μm fiber coupled to the 600-μm fiber using a power meter (model 210; Coherent Inc) at a known indicated power output from the dye laser. To verify that the same power was delivered at the tip of the cylindrically configured fiber, the same 400-μm fiber was placed into an integrating sphere (Labsphere, North Sutton, NH) and output was recorded. The normal 400-μm fiber was then replaced by the cylindrically emitting fiber, and the outputs were compared. If the fibers were coupled equally to the 600-μm fiber, the outputs recorded for the two fibers should be identical, ie, the emission profile of 100 mW/cm from a cylindrically tipped 400-μm fiber 1.5 cm long requires a measured output of 150 mW from the normal perpendicularly cleaved fiber. The indicated laser power associated with the measured output from the fiber would then be held constant to deliver the desired energy from the tip of the laser fiber for the duration of the treatment.

Laser Treatment

Bronchoscopic tumor illumination was performed under general anesthesia with on-line oximetry monitoring. Bronchoscopy was performed with a BF-1T Olympus bronchoscope, and an estimation of the degree of luminal obstruction was made and recorded photographically. The flexible bronchoscope was placed through the end of the endotracheal tube through a fiberoptic bronchoscope adapter (Portex, Wilmington, MA).

When the endobronchial lesion was viewed, the quartz fiber was loaded through the biopsy channel of the scope and negotiated near the tumor (Fig 1). Then the tumor was impaled by the quartz fiber (0.5, 1.0, or 1.5 cm) for interstitial illumination. Surface illumination was also performed when diffuse tumor not large enough to be impaled was present on the bronchial wall (3 patients) or if the tumor was too peripherally located to allow impaling (1 patient). Distal lesions necessitating bending the end of the bronchoscope into a J shape led to fiber fracture in 3 patients because of the inability of the fragile cylindrical fiber to negotiate the acute bend. Eventual fiber implantation was possible in 2 of the 3 patients; the third was treated with surface illumination.

Dose rate remained 400 mW/cm in all patients receiving interstitial treatment. Treatment energies are summarized in Table 2 and ranged from 150 to 250 J/cm (mean energy, 197 J/cm). After light delivery, the fiber was removed from the bronchus, and the area was examined for hemostasis and any obvious treatment effect. Extubation was performed in the operating room, and all patients were then returned to the surgical intensive care unit or recovery room for observation.

"Cleanup" Bronchoscopy

Seventy-two hours after laser treatment, 9 patients were returned to the operating room for "cleanup" bronchos-

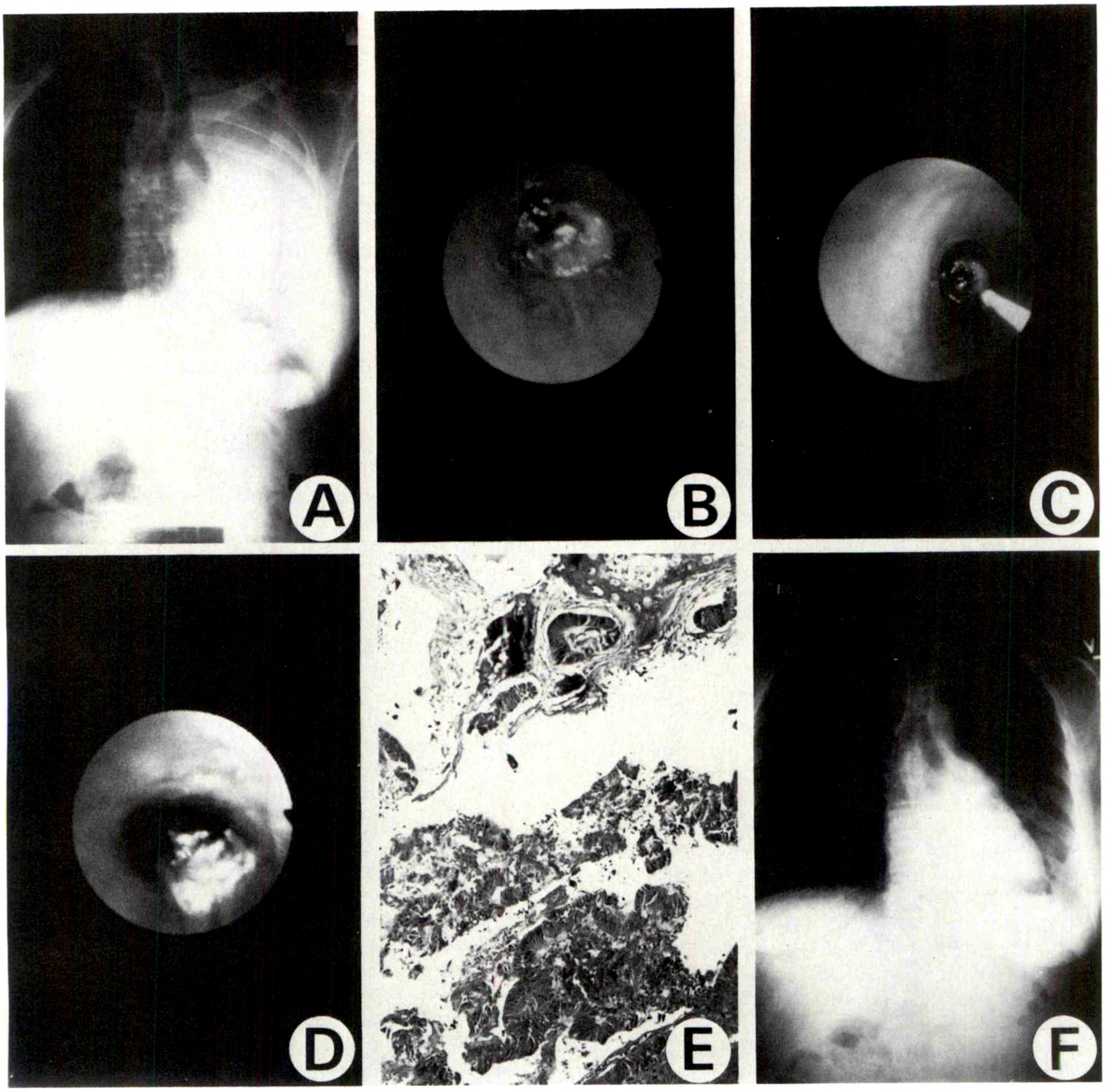

Fig 1. Patient with colon cancer metastatic to left main bronchus. (A) Chest roentgenogram made before treatment illustrating atelectatic left lung. (B) Endoscopic view of the tumor. (C) Laser fiber seen extending from bronchoscope just before interstitial implantation. (D) Luminal opening and tumor debris after endoscopic resection at 72-hour cleanup bronchoscopy. (E) Histology of resected tumor reveals areas of coagulation necrosis with intermixed viable cancer cells. (F) Chest roentgenogram made 6 weeks after photodynamic therapy demonstrates continued left upper and lingular expansion.

copy under general anesthesia. At this time, the treatment site was inspected and photographed. Using standard bronchoscope biopsy forceps, multiple fragments of avascular tumor were removed to establish luminal patency. Endobronchial resection was performed until biopsy of the tissue caused bleeding, which indicated that one was beyond the point of PDT effect. Hemostasis at the biopsy sites was easily controlled with lavage using iced saline solution or 1:100,000 epinephrine. Patients were then returned to the recovery room for postoperative monitoring after extubation. In 1 patient in whom pneumothorax developed after laser treatment, the cleanup bronchoscopy was performed 1 week after the PDT session (see Complications section).

Results

Characteristics of Treated Tumors at Cleanup Bronchoscopy

At the cleanup bronchoscopy in 8 of the 10 patients, the endobronchial tumor appeared paler in color than it was at the treatment bronchoscopy and was contracted. Bi-

Table 2. Treatment Variables

Patient No.	Time (min, s)	Dose (J/cm)	Fiber Length (cm)
1	10, 25	250	1.0
2	10, 25 R/2, 15 L	250/27 (S)	1.5
3	8, 20 L/9, 3 R	200/50 (S)	1.0/1.5
4	10, 25 L/10,25 L	250/250	0.5/1.0
5	6,15 L	150	0.5
6	10, 25 L/6, 15 R	250/150	1.0
	10, 25 L/5, 13 R	250/125	1.0
7	10, 25	250	1.0
8	8, 20	200	1.0
9	10, 25	250	0.5
10	10, 25	250 (S)	0.5

L = left; R = right; S = surface illumination.

opsy of these tumors was associated with a lack of hemorrhage, and endoscopic resection could be performed through the bronchoscope without airway bleeding.

Endobronchial Endoscopic Findings: Degree of Obstruction

Eight of the 10 patients had a substantial reduction in the degree of endobronchial tumor as assessed after the cleanup bronchoscopy (see Table 1). In the purely intrinsic situation, the degree of obstruction could be reduced from 80% to 12% (n = 6). Two patients with intrinsic lesions and extrinsic compression (melanoma and sarcoma) had no measurable relief of obstruction by PDT. In the patient with melanoma, the degree of light absorption by the melanin pigment precluded a satisfactory result. The sarcoma lesion, which was more hemorrhagic than the other tumors in the series, also probably attenuated light by scattering. Partial relief in the other patients with mixed intrinsic and extrinsic tumor could be achieved (75% before PDT to 33% after PDT) but was limited by the extrinsic component, which was most likely not effectively illuminated. Despite the lesser degree of the effective luminal opening in the group, distal airway examination (not possible before PDT in all 10 patients) could be achieved after PDT in 8 of the 10 patients.

Symptoms

Six of the 10 patients were symptomatic preoperatively (dyspnea necessitating oxygen in 4 and carinal stridor in 2. Of these 6 patients, 1 patient had no relief, 3 others had no further oxygen requirements, and the 2 patients with carinal stridor could be removed from positive-pressure ventilation and discharged from the hospital.

Roentgenographic Studies

Three patients had evidence of distal parenchymal collapse caused by the endobronchial lesion (lobar, 2; and total lung, 1). All 3 had reexpansion of the collapsed lung immediately after the cleanup bronchoscopy.

Histology of Photodynamic Therapy–Treated Tumors

Histological examination of the tissue fragments on the day of cleanup bronchoscopy revealed extensive coagulation necrosis intermixed with islands of viable tumor in 8 of the 10 patients. Two patients (1 with melanoma and 1 with sarcoma) had no evidence of effective treatment. Of the 8 patients with a treatment effect, 5 had repeat bronchoscopy 30 to 90 days after cleanup bronchoscopy; persistent nonobstructive tumor at the treatment bed was present in 3 of the 5 patients. One patient with lung cancer had no evidence of bronchial neoplasm on repeat biopsy 90 days after PDT, nor did another with metastatic renal cell cancer.

Subsequent Treatment After Photodynamic Therapy

Two patients (1 with metastatic colon cancer to the left mainstem bronchus and 1 with primary stage IIIA lung cancer) had sleeve resection 90 days after PDT. Both are alive without disease. Two patients have had local mediastinal radiotherapy after PDT, 2 patients had systemic chemotherapy, and no further therapy was offered to 4 patients (PDT nonresponders, 2; and carinal lesions, 2).

Complications

There were no complications during intravenous infusion of DHE and no instances of PDT–related skin sensitization. One patient who was treated for a carinal lesion after radiotherapy for lung cancer was discharged from the hospital but died of massive hemorrhage 77 days after PDT. Postmortem examination revealed extensive necrosis of subcarinal adenopathy, which had bled into the airway at the PDT site. Extensive pericardial and pleural carcinomatosis was also present.

In 2 patients treated for peripheral lesions, wedge-shaped, culture-negative pulmonary parenchymal infiltrates developed in the distribution of the segment treated; they resolved within 60 days after PDT (Fig 2). On the day after PDT treatment, 1 of these patients had a pneumothorax, which also resolved with chest tube drainage. It is theorized that these parenchymal complications represent a pulmonary effect of PDT, an effect possibly due to treatment of a peripheral bronchus. The chest roentgenograms reverted to pre-PDT status after the clearing of the infiltrates.

Survival

The 2 patients who did not respond to PDT had persistent respiratory symptoms and died 35 and 60 days after treatment (see Table 1). One other patient died of airway hemorrhage, as detailed in the Complications section. Three patients died of progressive systemic disease (111 days, 294 days, and 315 days) without recurrence of the respiratory problems. Four patients are currently alive, 2 after sleeve resection of all disease after PDT and 2 with successful palliation of segmental disease from renal cell cancer, 1 of whom is currently receiving immunotherapy.

Comment

The concept of a light-activated sensitizer for tumor cell diagnosis or killing is not new [6–8]. The treatment of

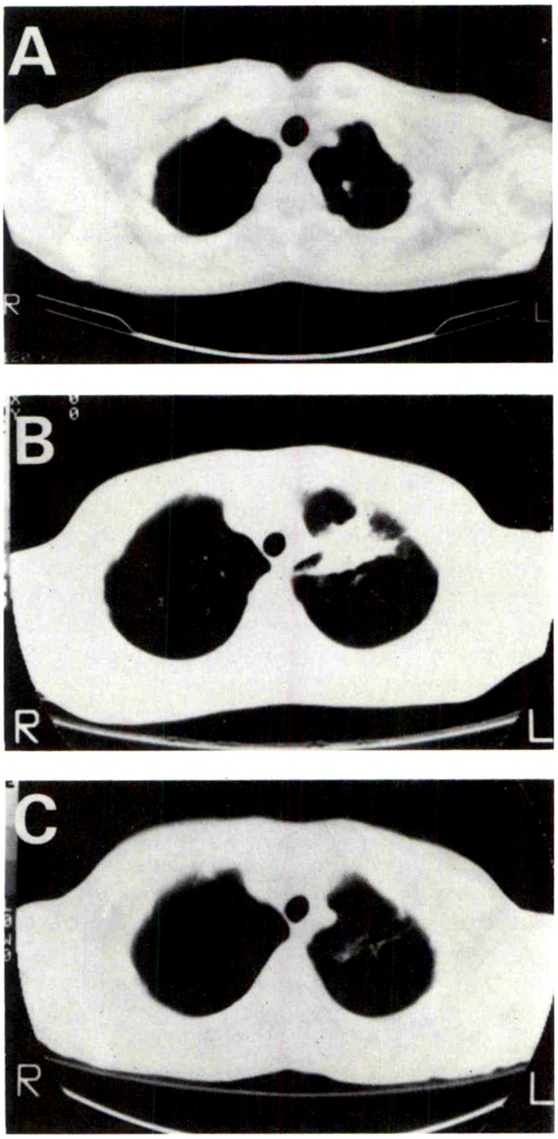

Fig 2. Reversible pulmonary infiltrate from peripheral endobronchial photodynamic therapy. (A) Computerized tomogram made before treatment of lesion in anterior segment of left upper lobe. (B) Infiltrate 2 weeks after treatment. (C) Healing of infiltrate 60 days after photodynamic therapy.

large numbers of patients with PDT to the bronchus, however, began only in the 1980s with reports from Balchum and Doiron [1], Hayata and associates [2], and Edell and Cortese [4]. All these investigators recognized the potential for relief of endobronchial obstruction with the use of PDT, which required the sensitizer (DHE), light (from an argon pumped-dye laser), and oxygen. These reports, although quite important in establishing the legitimacy of this treatment, were very difficult to interpret because of variation in the modes of treatment and the explanation of results.

The experience of Balchum and Doiron [1], the largest reported to date, makes the greatest attempt at standardization of treatment protocols with a consistent dose of hematoporphyrin derivative given to each patient (3 mg/kg). Light dose and dose rates, however, varied between patients, with 200 J/cm and 400 mW/cm used for cylindrical insertion, 50 to 100 J/cm^2 and 200 mW/cm^2 for surface illumination, and 200 J at 200 mW for point insertion needle technique. In a report describing 23 patients with early lung cancer treated with PDT, Hayata and coworkers [2] failed to standardize the dose of DHE (2.5 to 5 mg/kg) and had wide variations in light dose (90 to 500 mW/cm) and resulting energies (90 to 600 J/cm) even though they were treating patients with similar-stage tumors. Edell and Cortese [4], in a report of 38 patients from the Mayo Clinic, used varying doses of sensitizer (2.5 to 5 mg/kg) at varying intervals before treatment with wide dose rates and energies.

To compound the difficulty in interpreting these reports, the definition of a response has not been uniform. Balchum and Doiron [1] defined a complete response as an anatomical improvement in the endobronchial component, ie, the opening up of each involved bronchus completely to the walls, whereas the other two teams [2, 4] termed a complete response as no evidence of tumor histologically, cytologically, or endoscopically. A summary of the published results reflecting a wide variety of treatment protocols and response interpretations is seen in Table 3.

Our small series of patients reconfirms the ability of PDT to assist in the management of airway obstruction. Unique to our patients, however, is the similarity of patient treatment according to the treatment protocol with identical sensitizer concentrations being delivered and temporal addition of light at a uniform interval from sensitizer injection. All patients except 1 had interstitial therapy of the obstructing lesion at comparable dose rates (400 mW/cm) and energy (200 to 250 J/cm). This dose rate was chosen to provide expeditious energy delivery without thermal effects. Patients were carefully selected; all were required to have a component of the obstruction intrinsic to the bronchus. If one used the criterion of a complete response as airway opening with minimal residual obstruction (Balchum and Doiron [1]), our response

Table 3. Endobronchial Photodynamic Therapy

Reference	No. of Patients	Responses (%) Complete	Partial	None
Kato et al [9][a]	13	77	23	0
Kato et al [10, 11][b]	60	0	48[c]	52
Edell and Cortese [4]	30	70	30[d]	0
Doiron and Balchum [12]	38	34	66	0
Balchum et al [13]	22	91	9	0
Balchum [14]	236	100[d,e]	0	0
Vincent et al [15]	21	12	83	5
Forbes et al [16]	17	22	30	48
Lam et al [17]	7	80	20	0

[a] This study concerned early-stage bronchogenic cancer. [b] This study concerned advanced-stage bronchogenic cancer. [c] There was a residual tumor nest. [d] This response in this study was defined as airway open to bronchial wall. [e] This includes tumor metastatic to bronchus.

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rate with PDT would be 80%. However, the definition of a complete response as histological absence of tumor in subsequent biopsy specimens would be applicable in only 2 patients (20%). Failure to effectively treat 2 patients resulted from the inherent characteristics of the tumor (melanoma and hemorrhagic tumor), which caused light absorption or scattering.

In expert hands, laser of any sort may not be necessary for the management of malignant endobronchial obstruction. Mathisen and Grillo [18] recently presented their results with rigid endoscopic "core-out" of endobronchial lesions in 51 patients (13 with involvement of the mainstem bronchi). In their hands, this one session was 94% efficacious and was accompanied by minor hemoptysis (68%), arrhythmia (28%), pneumonia (12%), and pneumothorax (4%). For immediate airway relief, this technique may be as good as any laser technique; however, it involves only mechanical airway debridement without direct cytoxic effects. Future studies comparing the core-out technique with laser technique, either neodymium–yttrium-aluminum garnet (Nd–YAG) or PDT, must address the ability of such treatment to prevent further airway problems caused by regrowth phenomena either with or without supplementary adjuvant therapy such as chemotherapy or radiotherapy.

At present, there are no studies that directly compare the utility of other laser systems (Nd–YAG) with PDT. The Nd–YAG laser uses its wavelength transmission characteristic to provide coagulation of tissues through its thermal effects. As heating begins, power settings can be varied to choose between coagulation and denaturation or vaporization. This differs from PDT, which does not rely on thermal effects but on direct cytotoxicity of tumor as a result of the light–sensitizer interaction. Moreover, PDT is theoretically more selective because of selective retention of sensitizer in transformed (malignant) tissue compared with normal surrounding tissue. In experienced hands, the Nd–YAG laser for endobronchial therapy has become very safe, with decreasing rates of hypoxemia, airway perforation with uncontrollable bleeding, and airway explosion resulting from the thermal effects in an oxygen environment.

On the other hand, PDT, at present, is limited by the depth of penetration because of the wavelength properties of the sensitizer used and the chance for severe skin photosensitivity. Although PDT requires two bronchoscopic sessions (treatment and cleanup), these sessions are relatively short because of the avascularity of the tumor at cleanup, thus providing a bloodless field in which the tumor is endoscopically morcellated. To more easily define the morbidity and long-term airway effects of Nd–YAG therapy versus PDT, prospective randomized trials are now being performed. Our hope is that in the performance of such trials, the selection of patients will be similar in the adjuvant groups and that laser treatment will be uniform as it was in our series of patients with regard to sensitizer dose, energy input, and dose rate.

The goal of PDT in this series of patients was to be purely palliative. Of the 6 patients with symptoms, 5 were rendered asymptomatic from the respiratory obstruction, and none of the 5 had recurrent symptoms at follow-up or at the time of death. Three of these originally symptomatic patients were able to continue with further systemic or local therapy after PDT without threat of obstruction, as were 3 of the originally asymptomatic patients.

The combination of surgical resection after bronchial PDT as performed in 2 of our patients is not innovative; Kato and co-workers [11] reported that 13 patients had resection 1 to 9 weeks after PDT. The PDT was able to convert an inoperable situation into an operable one in 4 of 5 patients and to convert a pneumonectomy to a lobectomy in 7 of 9 patients. Whether this approach translated into a lengthening of survival is unknown.

General anesthesia was used in all 10 patients in this first series to allow complete airway visualization and accurate placement of the laser fiber without airway irritation. By controlling the patients' ventilation and abating the cough reflex, we could place the laser fiber with greater ease and maintain its position during the subsequent elimination without threat of dislodging. Endobronchial PDT, however, has been used in some series with topical anesthesia with good results. After our preliminary experience with general anesthesia and fiberoptic bronchoscopy, future protocols will incorporate topical anesthesia in select cooperative patients.

The PDT complications in our series reflect those reported by other investigators. Hemorrhage, usually from wall necrosis with mediastinal penetration, has been described to occur 4 to 5 weeks after PDT [3, 4]. Our patient who died 77 days after PDT essentially had necrosis of the previously irradiated medial wall of the right mainstem bronchus, with hemorrhage from chronically infected, necrotic mediastinal nodes. This radiation association was also pointed out by Balchum and colleagues [3], with 2 of 4 deaths related to hemorrhage occurring in patients previously treated with radiation therapy in addition to PDT. Edell and Cortese [4] related 3 deaths caused by exsanguination to very large, obstructive tumors. Both Balchum [14] and Hyata and colleagues [2] describe pneumothorax after PDT. There has been no description, however, of a reversible infiltrate in the lung as seen in 2 of our patients treated for peripheral tumors. We believe this represents the first documentation of a lung injury with endobronchial PDT, thus emphasizing the need for more accurate dosimetric observations, possibly with feedback dosimetry data incorporated in the treatment fiber through servo mechanisms.

Our lack of skin sensitization problems (sunburn) in sensitized patients reflects the importance of informing the patients of this possibility and providing suggestions on its circumvention. Patients are required to limit sun exposure for at least 4 weeks after they receive the sensitizer but may be exposed to incandescent light for up to eight hours a day. Dark sunglasses, wide-brimmed hats, long-sleeved shirts, neck scarves, long pants, shoes, socks, and gloves are all recommended if patients must go outdoors during the first 4 weeks. Sunscreens are ineffective in providing protection during the sensitization period.

What limits the extension of PDT to more innovative or aggressive modes of treatment at this time is the inability to reproducibly quantitate the effect of treatment as a function of dose of light and sensitizer used. Consistent results were obtained in this series of patients using a set sensitizer dose and light dose. The light dose, however, is measured at the tip of the laser fiber ex vivo, and to measure tissue effects as a function of energy input, on-line in vivo dosimetry must be perfected. Similarly, because the chance of accomplishing a complete histological response is remote with one treatment session, newer approaches must consider the possibility of repeat treatment at the time of cleanup bronchoscopy when adequate quantities of sensitizer may still be present in the tumor. We now have the ability to measure DHE content in excised tumor specimens, and this may add another dimension to dose accuracy in regard to sensitizer concentration for adequate treatment. To avoid the complications of normal tissue effects despite known lesser (but still measurable) quantities of DHE in normal tissues, we have initiated large animal studies to quantitate dose of sensitizer and light toxicity for endobronchial PDT.

As new sensitizers allowing greater penetration because of their longer wavelength become available, PDT may assume a more definitive role in the adjunctive treatment of extrinsic endobronchial malignancies. Prospective studies comparing the efficacy of argon PDT to Nd–YAG laser treatment are underway to determine the adequacy of tumor treatment and complication rate, and future prospective trials may compare surgical resection with bronchoscopic PDT for noninvasive superficial bronchogenic carcinoma, an approach that has been alluded to by the Mayo Clinic group [4] and the Japanese group [19].

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Carcinoma of the Esophagus: A Comparison of the Results of Transhiatal Versus Transthoracic Resection

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The cases of 78 patients with primary esophageal carcinoma treated from 1977 to mid-1987 were retrospectively analyzed. Fifty-two of the patients underwent transthoracic esophagogastrectomy (TTE) and 26, transhiatal esophagectomy (THE). The two groups were statistically similar in preoperative characteristics except that more of the THE group had received chemotherapy; this group had relatively more tumors of the upper esophagus; and 20 (77%) of the THE group, compared with 50 (96%) of the TTE group, had tumors in stages III and IV. The incidence of major postoperative complications did not differ significantly between the two groups. There were five (19%) anastomotic leaks in the THE group, but only one led to a prolongation of hospital stay by more than 14 days, whereas all three (6%) of the leaks in the TTE group caused hospital stay to be prolonged several weeks. Overall morbidity was high: 75% (39/52) for the TTE patients and 85% (22/26) for the THE patients ($p > 0.10$). Hospital mortality was 6% (3/52) in the TTE group and 8% (2/26) in the THE patients ($p > 0.10$). There was no significant difference in actuarial survival either between the two groups as a whole or between those patients in each group who had stage III or IV tumors. We conclude that THE, among the types of patients for whom we used the procedure, provides long-term survival comparable with that provided by TTE without causing a significant increase in hospital mortality or morbidity. In our hands, THE has been particularly useful in extending the indications for resection to poor-risk patients, such as those with chronic pulmonary disease, whom we formerly did not regard as being surgical candidates.

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The possibility that the esophagus could be bluntly stripped from the mediastinum was suggested by Denk [1] in 1913. Turner [2] performed the first successful removal of a carcinoma of the thoracic esophagus by a transhiatal technique in 1933. Antethoracic restoration of continuity was effected subsequently. Although more than 50 years have passed, the place that transhiatal resection deserves within the armamentarium of the surgeon treating esophageal carcinoma remains controversial. The procedure has the advantage of the avoidance of a thoracotomy, but many surgeons are wary of the possibility of tearing vital mediastinal structures and are concerned that the procedure may not provide an adequate removal of the cancer.

Several authors [3–7] have undertaken comparisons within their institutions of parallel series of patients, one treated by the standard transthoracic esophagogastrectomy (TTE) and the other, by transhiatal esophagectomy (THE). None of these studies have been entirely free from bias, and the results have been conflicting. To attempt to determine more definitively the merits and disadvantages of transhiatal resection in relation to standard transthoracic resection, we conducted our own retrospective study of 78 patients with esophageal carcinoma, 52 of whom were treated with the transthoracic approach and 26, by the transhiatal technique.

Material and Methods

Between January 1, 1977, and June 30, 1987, there were 96 consecutive patients who underwent esophagogastrectomy for carcinoma of the esophagus or cardia on the Thoracic Surgical Service of the University of Maryland Medical System/Hospital. Eighteen patients with carcinoma arising at the gastric cardia were excluded from further consideration because 16 of the 18 underwent resection through a left thoracotomy [7] and only 1 of the 18 had resection by the transhiatal technique.

Of the remaining 78 patients with carcinomas arising in the tubular esophagus who form the primary basis for this report, 52 underwent TTE. In 47 of these patients the approach was a standard combined right thoracotomy and laparotomy after the method originally popularized by Lewis [8]. In 3 additional patients, a cervical incision was added, and the esophagogastric anastomosis was performed in the neck. In the 2 remaining patients, the resection was performed through a left thoracotomy, with

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the addition of a small laparotomy incision in 1. In all 52 patients, the resection and the esophagogastric anastomosis were accomplished in one stage.

In 26 patients, a so-called blunt THE [9–11] was performed using only abdominal and cervical incisions. Nineteen of these patients were included in a previous report of 26 patients who underwent THE [11]. Six of the original 26 patients were excluded from the present study because they were operated on by a member of our division in other hospitals, and another was excluded because the tumor was located at the gastric cardia. The addition of 7 patients operated on since the earlier report brings the total to 26. In 25 of these patients, there was immediate restoration of continuity by a cervical esophagogastrostomy at the time of resection. The remaining patient underwent an urgent resection and died without having continuity restored.

The choice of operative technique was not specifically randomized. During the period 1977 through 1981, the transthoracic approach was the only technique employed. After THE was introduced in 1982, at first it was used principally for patients with carcinomas of the upper third of the thoracic esophagus and for patients with chronic pulmonary disease who were poor risks for a thoracotomy. The indications for the transhiatal approach were gradually expanded. During the latter years of the study period (1984 to mid-1987), THE was considered the technique of choice for neoplasms at all levels of the esophagus, provided the transhiatal inspection and palpation of the esophageal tumor during laparotomy did not show firm attachment or fixation of the tumor to the pericardium, aorta, or tracheobronchial tree. If firm fixation of the tumor was encountered, the transhiatal approach was abandoned and the transthoracic approach used instead. In 3 of the patients who underwent TTE, the transhiatal approach was attempted but had to be abandoned in favor of the transthoracic approach because of tumor adherence. In 1 additional patient, a tracheal laceration necessitated conversion to the thoracotomy approach.

The 58 patients who underwent TTE and the 26 who had THE were compared in terms of age, sex, preoperative weight loss, duration of symptoms, preoperative chemotherapy or radiotherapy (or both), and tumor location, cell type, and TNM stage (Table 1). The two groups also were compared with respect to the relative incidence of certain complications and hospital morbidity and mortality (Table 2). To eliminate the possible bias introduced by the fact that all of the transhiatal resections were done during the period 1982 to mid-1987 and the transthoracic resections throughout the 10.5-year period, the data from the 32 patients who underwent TTE during 1977 through 1981 were separately analyzed and compared with those of the 20 patients treated with TTE during 1982 to mid-1987. Also, survival data from those patients in the TTE group who had stage III or IV tumors were separately compared with those in the THE group who had tumors in the same stage.

For this study, hospital mortality was defined to include deaths within 30 days after operation, whether in or out of the hospital, and also deaths during the same hospitalization even though they may have occurred more than 30 days after operation. Up-to-date follow-up was possible for all 78 patients.

Table 1. Basic Clinical Characteristics of Each Group[a,b]

Variable	Transthoracic Esophago-gastrectomy (n = 52)	Transhiatal Esopha-gectomy (n = 26)	p Value
Age (yr)	55.7 ± 8.4	56.1 ± 6.4	NS
Sex			
Male	42 (81)	18 (69)	NS
Female	10 (19)	8 (31)	NS
Duration of symptoms (mo)	3.9 ± 3.4	4.4 ± 3.8	NS
Preop weight loss (% of weight before illness)	10.3 ± 7.5	7.3 ± 7.7	NS
Preop chemotherapy or radiotherapy	11 (21)	13 (50)	0.001
Tumor type			
Squamous cell	46 (88)	21 (81)	NS
Adenocarcinoma	0	2 (8)	
Adenocarcinoma in Barrett's esophagus	6 (12)	3 (12)	
Tumor level in esophagus			
Upper thoracic	2 (4)	9 (35)	0.001
Middle thoracic	41 (79)	12 (46)	
Lower thoracic	9 (17)	5 (19)	
Tumor stage			
0	0	2 (8)	0.001
I	0	3 (12)	
II	2 (4)	1 (4)	
III	34 (65)	14 (54)	
IV	16 (31)	6 (23)	

[a] Numbers in parentheses are percentages. [b] Where applicable, data are shown as the mean ± the standard deviation.

NS = not significant.

Pathological staging of the neoplasms was carried out according to the criteria set forth by the American Joint Committee on Cancer [12]. Discrete data were compared and analyzed using the χ^2 test or the Fisher exact test. The Wilcoxon rank sum test was used for comparisons involving continuous data. Actuarial survival curves were produced according to the Kaplan-Meier method [13]. Hospital deaths were included in the survival analysis. The log-rank test of Mantel [14] was used to compare survival curves.

Results

To conserve space, the comparative clinical data for the two subgroups of patients who underwent TTE during the two different 5-year periods are not included in the tables. Analysis of the preoperative data revealed that the only variable in which the two subgroups differed significantly was patient age. The average age for the earlier subgroup (treated during 1977 through 1981) was 58.2 ± 7.1 years and for the later subgroup, 51.6 ± 9.0 years (p =

Table 2. Complications According to Type of Operation[a,b]

Complication	Transthoracic Esophagogastrectomy (n = 52)	Transhiatal Esophagectomy (n = 26)	p Value
Splenic injury	8 (15)	4 (15)	NS
Pneumonia and/or respiratory insufficiency	20 (38)	14 (54)	NS
Empyema	5 (10)	1 (4)	NS
Anastomotic leak	3 (6)	5 (19)	NS
Vocal cord paralysis	5 (10)	3 (12)	NS
Temporary	1	2	
Permanent	4	1	
Delayed gastric emptying	2 (4)	1 (4)	NS
Renal	3 (6)	1 (4)	NS
Cardiac	6 (12)	3 (12)	NS
Neurological	4 (8)	1 (4)	NS
Infection of incision	2 (4)	3 (12)	NS
Intraoperative blood loss (mL)	1,819 ± 971	1,973 ± 1,167	NS
Length of operation (h)	8.2 ± 1.9	5.86 ± 1.7	0.001
Postoperative hospital stay (days)	26.7 ± 15.7	25.4 ± 17.7	NS
Death	3 (6)	2 (8)	NS
Complication rate	39 (75)	22 (85)	NS

[a] Numbers in parentheses are percentages. [b] Where applicable, data are shown as the mean ± the standard deviation.

NS = not significant.

0.017). In addition, in comparing the two subgroups in regard to the location of the tumor within the esophagus, the number of patients in some categories was too small to allow a valid test of significance of differences. No significant differences were noted between the two subgroups in regard to sex distribution, duration of symptoms, preoperative weight loss, preoperative chemotherapy or radiotherapy, tumor cell type, or tumor stage.

Therefore it was considered reasonable from a statistical standpoint to compare the overall group of 52 patients who underwent TTE during the entire 10.5-year period with the group of 26 patients who had transhiatal resection (see Table 1). This analysis showed no significant differences between the overall TTE and THE groups in regard to age, sex, preoperative duration of symptoms, preoperative weight loss, or tumor cell type. Patients with squamous cell carcinoma constituted more than 80% of each group. Six (12%) of the TTE group had adenocarcinomas, all arising in a Barrett's esophagus, and 5 (19%) of the THE group had adenocarcinomas, 3 of which arose in a Barrett's esophagus.

Only 11 (21%) of the 52 TTE patients had received preoperative chemotherapy or radiotherapy, whereas 13 (50%) of the 26 THE patients had received preoperative cisplatin–5-fluorouracil chemotherapy, with the addition of irradiation in 1 ($p = 0.001$). However, only 2 of the 13 had shown a complete response with eradication of all cancer from the surgical specimen (stage 0).

The two groups differed in terms of the location of the tumor in the esophagus ($p < 0.001$). Patients with mid-esophageal tumors predominated in both groups, but their predominance was greater (41 of 52 versus 12 of 26) in the TTE group. Whereas only 2 patients in the TTE group had tumors in the upper thoracic esophagus, 9 in the THE group had neoplasms at this level, including 1 whose tumor extended into the cervical esophagus and extrinsic larynx.

There was a significant difference ($p < 0.001$) between the TTE and THE groups in relation to tumor stage. Six of the tumors in the THE group were stage II or lower, but there were only 2 stage II tumors and no stage 1 or 0 neoplasms in the TTE group. In both groups, more than three fourths of the tumors (96% in the TTE group and 77% in the THE group) were stage III or IV.

There was no significant difference between the earlier (1977 through 1981) and the later (1982 to mid-1987) subgroups of patients who underwent TTE with respect to any of the complications listed in Table 2. Furthermore, when the combined overall TTE group of 52 patients was compared with the THE group, there was again no significant difference in the incidence of any of the complications. There was an unexplained high incidence (15%) of splenic injury necessitating splenectomy in both groups. Intraoperative complications that were limited to the THE group included an azygos vein laceration in 1 patient, which was repaired successfully through a sternotomy, and tears of the membranous trachea in 2 patients. In 1 of these patients, referred to earlier, a right thoracotomy was required for the repair and the transhiatal dissection was abandoned. In the other, the laceration was repaired through the cervical incision with a partial sternotomy extension.

The high incidence of pneumonia or respiratory failure in both groups is partly explained by the fact that the latter complication was defined simply as a need for mechanical ventilation for more than 72 hours.

There was a higher incidence of anastomotic leaks in the THE group but the difference was not significant, although it approached significance ($p = 0.065$). Four of the five cervical anastomotic leaks in the THE group healed spontaneously; none of the four resulted in a prolongation of hospitalization by more than 14 days. One of the four was simply a contained "diverticulum" at the anastomosis. In the fifth patient, the leak occurred at the pharyngogastric anastomosis after a laryngopharyngectomy, and required placement of a suture before it healed. On the other hand, all three of the leaks in the TTE group required several weeks to heal, and one resulted in an empyema.

The incidence of vocal cord paralysis was not significantly different in the two groups, but four of the five paralyses in the TTE group were permanent, whereas only one of the three in the THE group was permanent. This last instance of paralysis was, however, bilateral. All of the instances of permanent paralysis in both groups

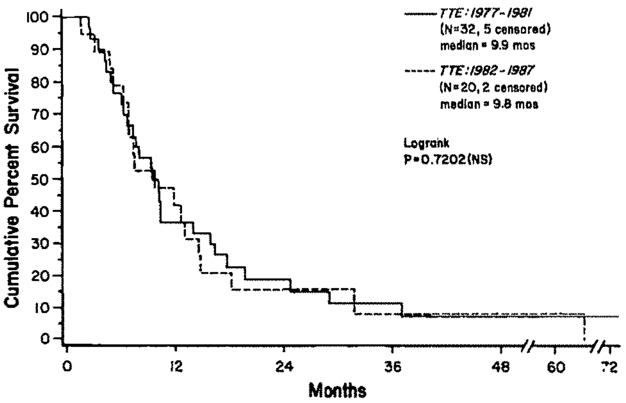

Fig 1. Actuarial survival curves for patients who underwent transthoracic esophagogastrectomy (TTE) *during 1977 through 1981 versus those who had the same operation during 1982 to mid-1987.* (NS = *not significant.)*

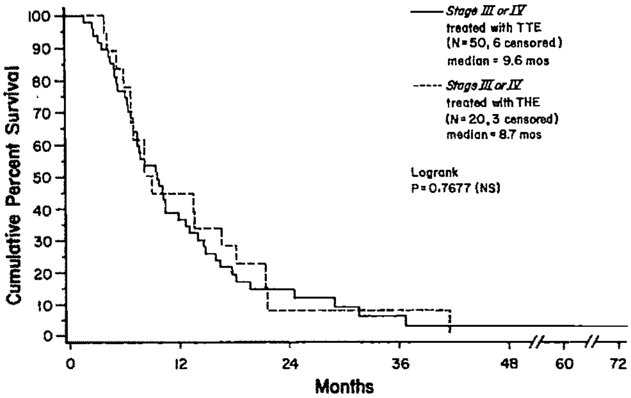

Fig 3. Actuarial survival curves for patients with stage III or IV tumors treated with transthoracic esophagogastrectomy (TTE) *versus those with tumors in the same stages who underwent transhiatal esophagectomy* (THE). (NS = *not significant.)*

occurred in patients with carcinomas of the upper or middle thoracic esophagus in whom the dissection was carried close to the recurrent nerve in an effort to encompass the tumor.

The length of operation was significantly less in the THE patients ($p < 0.001$), but intraoperative blood loss and average postoperative hospital stay were not significantly different between the two groups. Our mean blood loss of 1,973 mL for the THE group is higher than that generally reported [9, 10]. The mean was affected by 4 patients whose blood loss was in excess of 3,500 mL: the 1 patient with a laceration of the azygos vein, 2 patients with hepatic disease and engorged periesophageal veins, and 1 patient who had an active esophagitis with dense adhesions to surrounding structures. The rather lengthy mean hospital stay in both groups is partly attributable to social factors: many of our patients had inadequate family support and therefore had to remain hospitalized until they were able to care for themselves.

The overall morbidity or complication rate, defined as the number of patients who had one or more complications, was high in both groups: 39 (75%) of 52 for the TTE group and 22 (85%) of 26 for the THE patients ($p > 0.10$).

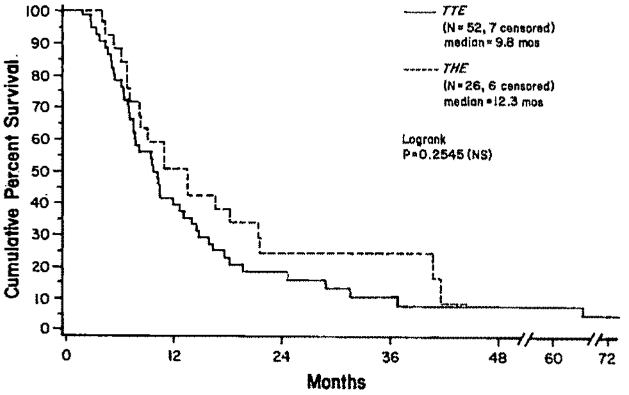

Fig 2. Actuarial survival curves for the overall group of patients who underwent transthoracic esophagogastrectomy (TTE) *versus those who underwent transhiatal esophagectomy* (THE) (NS = *not significant.)*

The high rate can be partly explained by the fact that our definition of complication was rather liberal and included such incidents as pleural entry during transhiatal dissection that necessitated chest tube insertion.

Hospital mortality was 3 (6%) of 52 in the TTE group and 2 (8%) of 26 in the THE group ($p > 0.10$). Of the 3 deaths after TTE, 1 resulted from adult respiratory distress syndrome, 1 from a cerebrovascular accident, and 1 from empyema, sepsis, and multisystem failure. Of the 2 deaths in the transhiatal resection group, 1 occurred on the second postoperative day as a result of cardiac arrest related to severe coronary artery disease. The other involved a woman who was operated on urgently for a perforated carcinoma that had led to empyema. The patient's condition was too precarious for restoration of gastrointestinal continuity. Her condition continued to deteriorate, and she died of multisystem failure 32 days after operation.

In analyzing the actuarial survival, no significant difference was noted between the earlier (1977 through 1981) and the later (1982 to mid-1987) subgroups among the TTE patients ($p > 0.10$ by log-rank test) (Fig 1). The earlier subgroup showed a median survival of 9.9 months and a mean survival of 13.6 ± 1.9 months (± standard deviation). The later subgroup showed corresponding figures of 9.8 months and 15.2 ± 3.9 months.

Analysis of the actuarial survival of the overall TTE group in comparison with the THE group again showed no significant difference ($p > 0.10$ by log-rank test) (Fig 2). The median survival was 9.8 months and the mean survival, 15.4 ± 2.3 months for the TTE group, and the corresponding figures were 12.3 months and 18.1 ± 2.9 months for the THE group. Comparison of the actuarial survival for the patients with stage III or IV tumors in the overall TTE group showed no significant difference from those in the THE group who had tumors in the same stages ($p > 0.10$ by log-rank test) (Fig 3).

Comment

There are certain differences between our series and those of other authors who have compared the results of TTE and THE within a single hospital. Garvin and associates [3, 4] compared transhiatal with transthoracic resection, and found that the former resulted in greater morbidity and inferior palliation. However, they restored continuity after transhiatal resection with either a retrosternal gastric tube or the whole stomach. Steiger and Wilson [5] favored the transhiatal approach even though they encountered two deaths, four anastomotic leaks, and two recurrent laryngeal nerve injuries among 20 patients treated with this technique compared with no deaths, no leaks, and no recurrent nerve injuries among 21 patients who underwent transthoracic resection. Neither group of authors compared the two techniques in terms of actuarial survival.

Goldfaden and co-workers [6] limited their study to patients with adenocarcinoma of the distal esophagus or gastric cardia. They compared a group of 43 patients who underwent a standard TTE with a similar group of 29 patients who underwent THE and proximal partial gastrectomy. Many of the patients who underwent the transthoracic procedure were operated on during an earlier 10-year period before the transhiatal technique was introduced. The perioperative mortality, the perioperative complication rate, the average operative blood loss, and the average postoperative stay were all greater after transthoracic resection. There was no significant difference in survival between the two groups.

Shahian and associates [7] analyzed 95 patients with carcinoma of the esophagus, exclusive of carcinoma of the gastric cardia, who were treated during a 6.5-year period: 65 underwent transthoracic resection, and a statistically similar group of 30 had transhiatal resection. In addition to the 30 patients who underwent THE, there were 10 other patients in whom the procedure was attempted but abandoned in favor of the thoracotomy approach. The overall morbidity was significantly higher in the transhiatal group. The hospital mortality was higher in the transhiatal group (13%) than in the transthoracic group (6%), but the difference was not significant. When the combined morbidity and mortality of certain subgroups within the transthoracic and transhiatal groups were compared, significant differences were found that favored transthoracic resection. There was no difference in actuarial survival either between the two groups as a whole or between those in each group who had stage I or stage III tumors.

In our series, there were some potential sources of bias that needed to be addressed before we could meaningfully compare the two techniques. First, the fact that the transhiatal resections were performed only during the last 5.5 years of the 10.5-year period covered by the transthoracic resections was dealt with by comparing the two subgroups of patients who underwent transthoracic resection during the earlier (1977 through 1981) and later (1982 to mid-1987) periods. The two subgroups differed only to the extent of a 6.6-year disparity in average age. Further, there was no significant difference in the actuarial survival of the two subgroups (see Fig 1).

When the overall transthoracic group was compared with the transhiatal group, it was found, first of all, that more of the transhiatal group had received chemotherapy. We believe it is unlikely that the greater use of chemotherapy in this group materially influenced their outcome. Only 2 of the 13 who received chemotherapy were complete responders. To date, we are not aware of any reported randomized series in which adjuvant chemotherapy followed by resection provided superior long-term survival to that afforded by resection alone [15]. Second, if the greater proportion of patients with upper-third tumors in the transhiatal group had any effect at all on their outcome, it likely was an unfavorable one. Skinner and associates [16], in their series of en bloc esophagectomies, found that the level of the tumor within the esophagus was not an independent predictor of outcome. On the other hand, the experience of Orringer [10] with THE appeared to indicate that the higher the location of the tumor within the esophagus, the shorter the survival. Last, we think that the effect of the relatively smaller proportion of patients in the transhiatal group who had tumors in stages III and IV has been obviated by our comparison of only those patients with tumors in these stages in each group. There was no difference in actuarial survival (see Fig 3).

It is probably impossible to eliminate all bias from a study of this nature. A prospectively randomized, controlled evaluation would be required, and most hospitals do not treat enough patients with esophageal carcinoma to make this feasible.

To summarize, we found in this study that, with the method of selection of patients for THE that we have employed [11], the procedure provides long-term survival comparable with that provided by TTE without an attendant significant increase in hospital mortality or morbidity. We therefore believe that THE merits a very definite place in the armamentarium of the surgeon treating esophageal carcinoma. We do not think that transhiatal resection deserves to be virtually the sole technique of resection used, as it apparently is in the practice of Orringer [6, 9, 10]. Nor do we think it should be considered categorically contraindicated for lesions of a certain stage or location, as for example, T3 tumors of the upper esophagus [17].

To our minds, one of the greatest advantages of THE is the fact that it enables us to perform resection on patients with carcinomas of the upper third of the esophagus who have pulmonary functional impairment and who would tolerate a thoracotomy poorly. We agree with Murray [18] that the issue should not be transhiatal *versus* transthoracic esophagectomy, but the selective application of the technique that is ideal for a particular patient. The surgeon performing THE should be adept in both the transhiatal and the transthoracic techniques and should be able to change promptly to the latter approach if he or she encounters an unfavorable lesion during transhiatal dissection.

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Right Gastroepiploic Artery: A Third Arterial Conduit for Coronary Artery Bypass

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Experience with 39 patients (32 men, 7 women) undergoing coronary artery bypass grafting with the right gastroepiploic artery (RGEA) is reported. Indications initially included poor-quality or absent saphenous vein, ascending aortic atherosclerosis, and repeat coronary artery bypass grafting. The average number of grafts per patient was 4.10. Arteries bypassed were the posterior descending (22 patients), right coronary (12), diagonal (5), and marginal (4). Distal RGEA internal diameters of all grafts measured 1.5 to 3.25 mm (average diameter, 2.14 mm). Pedicled graft lengths measured 18 to 30 cm (average length, 23.7 cm), and free grafts, 8 to 24 cm (average length, 17.7 cm). In 6 patients, no vein grafts were used, and in all patients, at least one internal mammary artery graft was placed. Early postoperative cardiac catheterization (19 pedicled and ten free grafts) in 29 patients revealed all grafts to be patent without a kink or twist, but three of these free RGEA grafts had vasospasm. Advantages of RGEA grafts are as follows: (1) it is a third arterial conduit with artery–artery anastomoses of comparable sizes; (2) a shorter leg incision or no leg incision is necessary; (3) it can be harvested simultaneously with the internal mammary artery and the saphenous vein; (4) the proximal anastomosis (free grafts) is easy; (5) its use avoids bilateral internal mammary artery grafts in patients at high risk for sternal infection; and (6) atherosclerotic ascending aortas are not clamped. Subintimal hyperplasia and atherosclerosis of RGEA grafts are unlikely. There are several disadvantages to the RGEA grafts: (1) the abdominal cavity must be entered; (2) the graft is not available after a gastric operation; (3) there is the possibility of graft damage with future abdominal procedures; (4) operating time is longer; and (5) at present, long-term patency and adequacy of flow are uncertain. Some important technical features of the operation include: (1) careful pericardial entry of pedicled grafts; (2) multiple tacking sutures for RGEA grafts; (3) marking the pedicle to avoid twists or kinks; (4) large RGEA branch ligation rather than clipping or cautery; and (5) intraluminal infusion of dilute papaverine hydrochloride to dilate the grafts before cardiopulmonary bypass.

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There has been a major change in the choice of conduit for coronary artery bypass grafting (CABG) in the last 10 years. The "gold standard" for choice of conduit has changed from the saphenous vein graft to the internal mammary artery (IMA) graft [1]. Not only have long-term studies found that the IMA graft is superior in patency, but also it is now clear that it is the superior graft in terms of longevity [2].

The improved patency rate of the IMA graft over the saphenous vein graft has not been adequately explained. The importance of the increased IMA wall synthesis of prostacyclin is apparent and may be a biochemical explanation for the higher patency rate of IMA grafts [3]. Our studies comparing the synthesis of prostacyclin in the IMA, saphenous vein, and right gastroepiploic artery (RGEA) walls is the subject of another report.

With more complex CABG operations and an increased number of reoperations facing cardiac surgeons, there is a struggle in a substantial number of instances to obtain an adequate amount of acceptable graft material. Having a third conduit available, such as an RGEA graft, is attractive, especially if the long-term patency in this arterial graft approaches that of the IMA graft. The purpose of this report is to present our experience in 39 patients in whom the RGEA served as a third arterial conduit for CABG.

Material and Methods

During a 1-year period, the RGEA was used in 39 patients (32 men, 7 women) for CABG, with a minimum follow-up of 1 month. Age ranged from 41 to 77 years (average age, 58.5 years). Body surface area ranged from 1.53 to 2.46 m^2 (average area, 1.90 m^2).

There were 43 concomitant IMA grafts placed, and 7 patients had extensive endarterectomies with specimens 6 cm or greater in length. There were 26 pedicled grafts and 15 free grafts performed, a total of 41 RGEA grafts in the 39 patients. Two patients had sequential RGEA grafts. Distal anastomoses were placed to the right coronary artery in 12 patients, to the posterior descending in 22, to the diagonal in 5, and to the marginal circumflex branch in 4, a total of 43 coronary arteries bypassed.

Postoperative angiographic studies were performed before discharge in 28 patients. Serum amylase levels were measured 12 to 24 hours postoperatively, and if the levels were elevated, the measurements were repeated daily until they returned to normal.

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Table 1. Indications for Right Gastroepiploic Artery Grafting in 39 Patients

Indication	No. of Patients
Double amputee	1
Severe bilateral leg burn scars	1
Diseased ascending aorta	9
Poor-quality saphenous vein	11
Young age	7
Leg edema	1
Severe peripheral vascular disease of the leg	3
Reoperation	3
Ideal anatomy[a]	3

[a] Patients had 100% occlusion of the right coronary artery and a perfect size match between that artery and the right gastroepiploic artery.

Incisions in the linea alba were initially extended inferiorly 7.62 to 10.16 cm, but toward the end of the study, this was reduced to no more than 2 inches (5.08 cm). Linea alba closure was accomplished with interrupted sutures. No abdominal drains were used. Free flow of the RGEA grafts was only randomly measured. The primary goal in this study was to obtain the proper graft length, orientation, and anastomotic site.

Initially, indications for use of the RGEA were absence or poor quality of the saphenous vein, reoperation, and atherosclerotic disease in the ascending aorta. Later in the study, indications were liberalized to include young age, severe lower-extremity atherosclerosis, severe leg edema, and the angiographic finding of 100% occlusion of a medium-sized right coronary artery (Table 1). In each patient the abdomen was examined preoperatively for bruits in anticipation of any possible atherosclerosis of the celiac artery. No patient had symptoms of mesenteric artery insufficiency. The only prior upper abdominal operation encountered in this group of patients was cholecystectomy through a subcostal incision. A lower abdominal procedure was not a contraindication for use of the RGEA graft.

Internal diameter of the proximal RGEA was estimated with calibrated probes when pedicled grafts were used and accurately measured when free grafts were used. Distal RGEA internal diameter was accurately measured and recorded for all grafts at the anastomotic sites. The length of all grafts was recorded. Intraluminal infusion of dilute papaverine hydrochloride (60 mg in 40 mL of normal saline solution) was used to dilute the RGEA grafts before cardiopulmonary bypass. Detailed technical aspects of grafting the RGEA to coronary arteries have been reported [4].

Results

In no patient was the RGEA found to be totally unacceptable at operation and use of the artery abandoned. Likewise, no patient had to be turned down for RGEA grafting because of preoperative bruits found high in the abdomen on auscultation. The pedicled graft lengths measured 18 to 30 cm (average length, 23.7 cm). These lengths were shortened with experience and thereby, larger distal anastomotic RGEA internal diameters achieved. Free graft lengths ranged from 8 to 24 cm (mean length, 17.7 cm). The estimated internal diameters of the pedicled RGEA grafts near the origin from the gastroduodenal artery ranged from 3.5 to 5 mm (average internal diameter, 4.02 mm). Internal diameters of the distal RGEAs (pedicled and free grafts) measured 1.5 to 3.25 mm (average internal diameter, 2.14 mm), indicating acceptable sizes for distal anastomoses. In 2 patients, the RGEA was long enough to be used for two grafts. Six patients had no vein grafts.

There were 3 deaths in the series. None could be attributed to use of the RGEA. One patient had unrecognized liquefied ascending aortic atherosclerotic debris and died secondary to embolization of cholesterol atheromatous material. A hypertensive patient had a postoperative cerebrovascular accident in the same hemispheric area of a previous preoperative stroke. Extension of the stroke on the second postoperative day resulted in death 1 week later. Another patient with no available vein from any site because of previous CABG sustained an acute myocardial infarction and underwent operation in cardiogenic shock. Both IMAs and the RGEA were the only graft material available and were harvested during resuscitative efforts.

Three patients had transient rises in serum amylase levels. Two of these patients had ileus, with mild pancreatitis being suspected in one. Hospitalization was prolonged four days in that patient. During the study period, ileus and mild pancreatitis developed in another patient who did not have a laparotomy or undergo grafting with the RGEA, and was not part of the study. Minimally bloody nasogastric aspirate was noted in the first six to eight hours in almost all patients, but did not inhibit the taking of fluids orally within 24 hours after operation. Other than one pneumothorax, there were no other major hospital complications. In 1 patient on a regimen of warfarin sodium, late pericardial tamponade developed after hospital discharge but was successfully treated after the patient was readmitted.

Early postoperative angiographic studies (1 to 3 weeks) were performed in 29 patients either by flush celiac injection or, less often, by selective RGEA angiography. Nineteen pedicled grafts and ten free RGEA grafts were found to be patent without a kink or twist (Table 2). An unexpected finding was that three of these 10 free RGEA

Table 2. Results of Postoperative Angiography of 41 Grafts in 39 Patients

Result	Pedicled Graft	Free Graft	Total
Patient	19	10[a]	29[a]
Spasm	0	3	3
Occlusion	0	0	0
Not restudied	7	5	12
Total	26	15	41

[a] Three of these grafts were the ones with vasospasm.

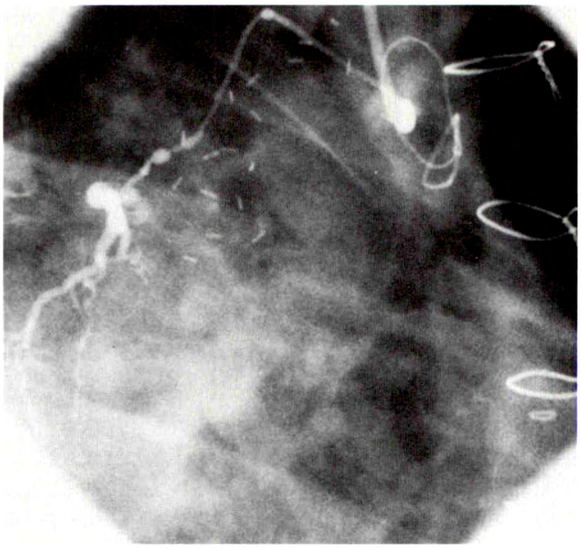

Fig 1. Vasospasm along the course of a free RGEA graft to a diagonal coronary artery six days after coronary artery bypass grafting. Two additional free RGEA grafts with vasospasm early postoperatively did not have an irregular appearance along the graft as seen here.

grafts had major vasospasm (Fig 1), the etiology and long-term fate of which are uncertain. Postoperative follow-up has revealed all patients to be free from angina and abdominal symptoms. There have been no early or late wound problems.

Comment

The RGEA was first used as a direct bypass graft to the right coronary artery in January 1974 by Dr W. Sterling Edwards of Albuquerque, NM (Dr W. Sterling Edwards. Personal communication, July 28, 1988). Dr Edwards and associates [5] began working with abdominal–coronary artery bypass in the early 1970s, and had planned a splenic artery bypass in a 56-year-old man in conjunction with bilateral IMA bypass grafting. All saphenous vein had been stripped because of varicosities, and the splenic artery was found to have an aneurysm; therefore, the RGEA was used for a direct bypass through the diaphragm to the right coronary artery. The patient was lost to follow-up after 1 year [5].

Carter [6] in 1987 reported 30 consecutive patients undergoing CABG using pedicled RGEA grafts. Arteries bypassed were the posterior descending branch of the right coronary and distal circumflex. Pym and colleagues [7] presented their experience with pedicled RGEA CABG in 9 patients. Their study began in June 1984 and was reported in 1987. After examining the lengths and sizes of the RGEAs in 100 angiograms, Suma and co-workers [8] extended the use of the operation to the left anterior descending system. Lytle and associates [9] reported use of the RGEA as a pedicled graft in 17 patients and its use as a free graft in an additional 19 patients. All three major coronary systems were bypassed by this group.

A review of the literature including the patients reported here provides a total of 118 patients [10]. Fifty-eight grafts were restudied 1 week to 13 months postoperatively, and 56 (97%) were patent (Table 3). After early experience with the IMA as a coronary artery bypass graft, a number of investigators began to question the adequacy of IMA flow. Over the years, it has become clear that the IMA flow is certainly adequate. Probably in many instances, flow was questioned by surgeons early in their experience because of technical errors, as IMA grafting is more technically demanding than saphenous vein graft procedures.

Flow characteristics of the RGEA grafts have yet to be investigated. Because of the long length of the RGEA, surgeons should be aware of the possibility of competition of flow when the RGEA is used to bypass less critically stenotic (50% to 70%) coronary arteries. Certainly there will be a learning curve to ensure adequate RGEA graft flow, although a standard technique for the operation has been developed. The RGEA is a relatively long graft when used as a pedicle and may well have a lower flow than the shorter IMA grafts. The data of Carter [6] revealed that 25 of 30 patients complained of early postoperative symptoms suggestive of angina, but became symptom free with normal exercise tolerance in the late postoperative period. Perhaps RGEA grafts will increase in size on demand as do IMA grafts.

The influence of interrupting lymphatic and venous drainage with harvest of RGEA grafts is unknown. We have observed on occasion that the primary venous drainage of the RGEA is interrupted during harvest of the graft. With ligation of this venous drainage, we have occasionally noted edema in the distal pedicle at the time of sternal closure. We have also noted that the RGEA graft appears to be more prone to vasospasm than the IMA graft. Further late postoperative angiographic studies of our 3 patients with early free RGEA graft spasm will provide important data. The use of the free graft (Fig 2) at this time must be tempered with this in mind.

Histologically, we have noted a difference in the RGEA compared with the IMA. With elastic staining, more

Table 3. Postoperative Right Gastroepiploic Artery Graft Patency

Reference	No. of Patients	No. of Grafts Restudied	Patency
Edwards [personal communication][a]	1	0	. . .
Carter (Australia) [6]	30	9	7
Pym et al (Canada) [7]	9	8	8
Suma et al (Japan) [8]	2	2	2
Lytle et al (USA) [9]	36	9	9
Buffolo et al (Brazil) [10]	1	1	1
Mills and Everson (USA) [present report]	39	29	29[b]
Total	118	58	56 (97%)

[a] See text for details (Comment section). [b] Three free grafts had vasospasm.

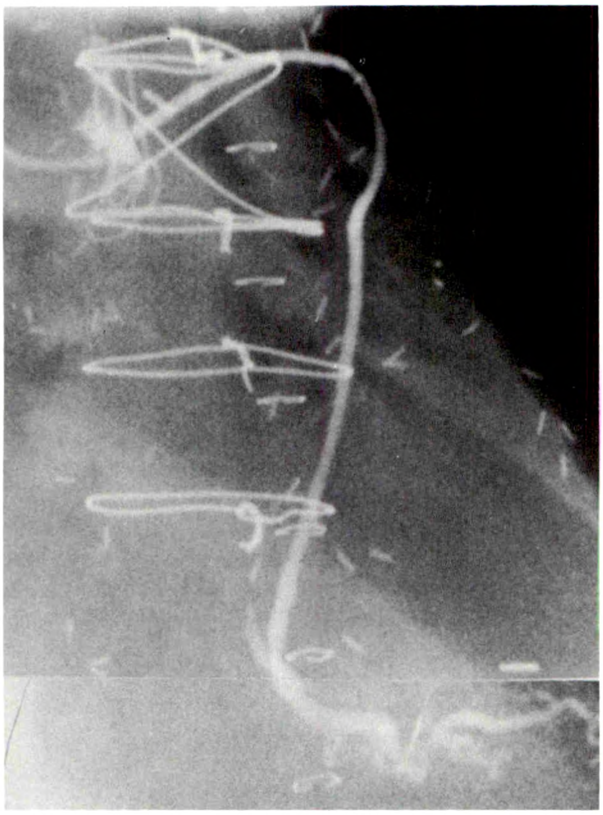

Fig 2. *Free right gastroepiploic artery graft to the marginal branch of the circumflex coronary artery.*

elastic tissue is found in the media of the IMA graft, as opposed to essentially an absence of elastic tissue in the media of the RGEA. At this time, the importance of this finding correlated with our observed vascular spasm is unknown.

The possible abdominal complications have been addressed [9]. Intraabdominal bleeding in the early period after cardiopulmonary bypass may be difficult to recognize, and for that reason, we have been prone to ligate gastric branches of the RGEA that will remain in the abdomen as opposed to relying on clips, which have a tendency to come off. We suspect that the abdominal symptoms noted in 2 patients in the early postoperative period in our series were related to dissection down into the origin of the RGEA from the gastroduodenal artery with possible ligation of a small pancreatic branch. The mortality of 7.6% in this series is comparable with that reported by Lytle and co-workers [9].

Indications for RGEA coronary artery bypass began with our first patient, a young, male posttraumatic double amputee. Nine patients had a diseased ascending aorta, and RGEA grafting allowed us to avoid clamping the diseased areas on the ascending aorta with the known complications. Severe bilateral leg burn scars with skin grafting provided a clear indication for RGEA bypass in 1 patient, as did major leg edema in another patient. Poor-quality saphenous veins with varices, prior phlebitis, or small saphenous vein size was an indication for RGEA grafts in 11 patients. Three patients in this series had severe lower-extremity peripheral vascular disease with obvious poor healing potential. Three patients were undergoing repeat CABG for vein graft failure. Seven patients had a combination of these indications.

With greater experience, our indications have been extended to include young patients because of the anticipation of improved longevity with an arterial rather than a venous graft (7 patients). In 3 patients, the anatomy of the right coronary system with 100% occlusion and a perfect size match of the RGEA led to the use of that graft (Fig 3).

A number of technical points deserve mention. The nasogastric tube is positioned when the abdomen is opened to avoid manipulation of the stomach later during the operation, which might avulse ties or clips. A small Balfour retractor with the bladder blade placed inferiorly is used for exposure of the abdomen. The IMA, RGEA, and saphenous vein can be harvested simultaneously. If abdominal thrills are palpated in the region of the celiac axis, the decision may be made to use the RGEA as a free graft. The anterior layer of the greater omentum can be teased off anterior to the RGEA with the spatula of the

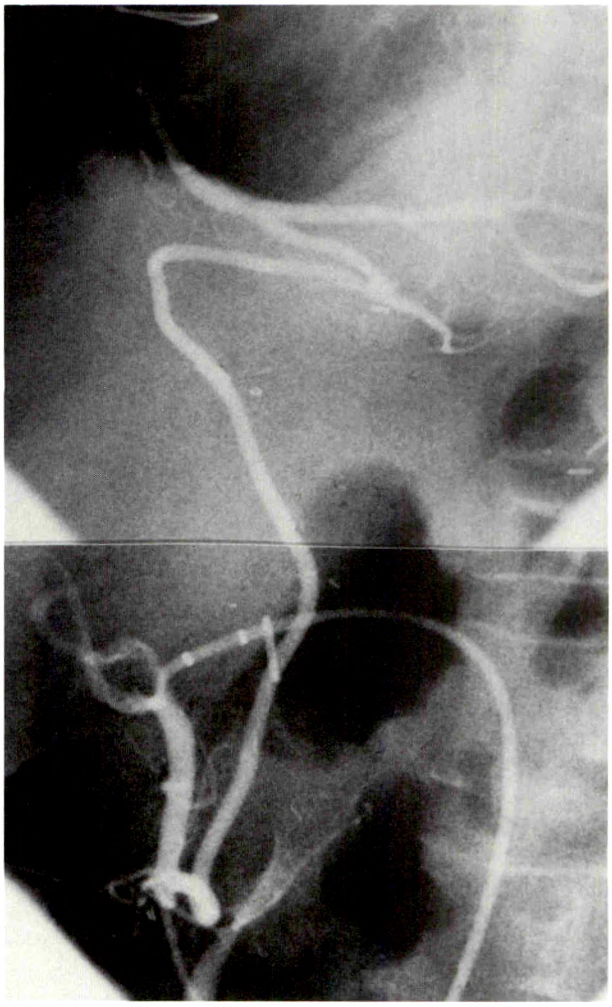

Fig 3. *Postoperative angiogram of a pedicled right gastroepiploic artery graft to a right coronary artery with 100% occlusion.*

electrocautery before ligation of the gastric branches. This will allow an RGEA pedicle that is less bulky with fat.

Ligation of anterior and posterior gastric branches of the RGEA in a single bundle will reduce the available length of the graft if they are anatomically separated, as is found in some patients. Dissection is carried proximally to the origin of the RGEA and dissection around or ligation of the anterior superior pancreaticoduodenal artery is avoided. As it is harvested, the RGEA graft is marked lengthwise on one side using a double-armed silk suture. This marker is extremely helpful in avoiding twists in the graft.

The pedicled graft can be routed anterior to the duodenum or, more commonly, posterior to the stomach through the lesser sac and then through the avascular space of the lesser omentum. The approach to the pericardial cavity is most often anterior to the left lobe of the liver and through a 2-cm^2 window in the diaphragm slightly to the right of the midline (see Fig 3). If the graft is routed to marginal branches on the obtuse margin of the heart, the triangular ligament is divided for a posterior approach to the pericardium under the left lobe of the liver. That ligament is tacked to the diaphragm anterior to the graft to prevent compression. Intraluminal infusion of papaverine is used to dilate the graft. The graft is tacked at multiple sites after it enters the pericardium, especially with heavy, fat RGEA pedicles. The pedicled RGEA graft is not routed over the middle of the stomach to avoid potential tension with gastric dilation. The greater omentum is brought up anteriorly to cover the stomach before the abdomen is closed with interrupted linea alba sutures. The RGEA–coronary artery anastomoses are performed last. An 8-0 polypropylene suture is used with the same suturing technique as for IMA grafts (Fig 4).

Use of the RGEA graft is especially advantageous in patients with poor-quality or absent saphenous vein. A strong indication for its use in a patient is early postoperative failure of saphenous vein grafts without correctable cause, ie, subintimal hyperplasia. Use of the RGEA graft in a diabetic patient avoids bilateral IMA graft operations in which there is a higher incidence of sternal infection. When there is substantial disease in the ascending aorta and a "no touch" technique is used [11], the RGEA pedicle represents a third arterial graft. In 33% of patients, the RGEA is long enough that a short free graft can be used in addition to a standard pedicled graft [8]. On occasion, the surgeon may wish to save the left IMA for possible future use in a young patient who has a large left anterior descending coronary artery that does not need a bypass graft. The RGEA graft in that setting allows use of an arterial rather than a venous conduit to other coronary arteries in patients with potentially longer life expectancies. Shorter leg incisions are possible with multiple bypass grafting when the RGEA is used.

A distinct disadvantage of use of the RGEA is that the abdominal cavity is entered, which leads to probably rare yet inherent problems. A future abdominal operation could damage an RGEA graft. Though unlikely, possible long-term gastric or nutritional ill effects are unknown. Unrecognized abdominal aortic or celiac atherosclerosis is more difficult to assess, as opposed to subclavian disease with use of the IMA [12]. Operating time is longer, and late patency of the RGEA graft is unknown. A twist in the RGEA graft is likely without meticulous care, as opposed to pedicled IMA grafts. Hematoma in RGEA pedicles is technically troublesome, and control of bleeding can jeopardize the graft.

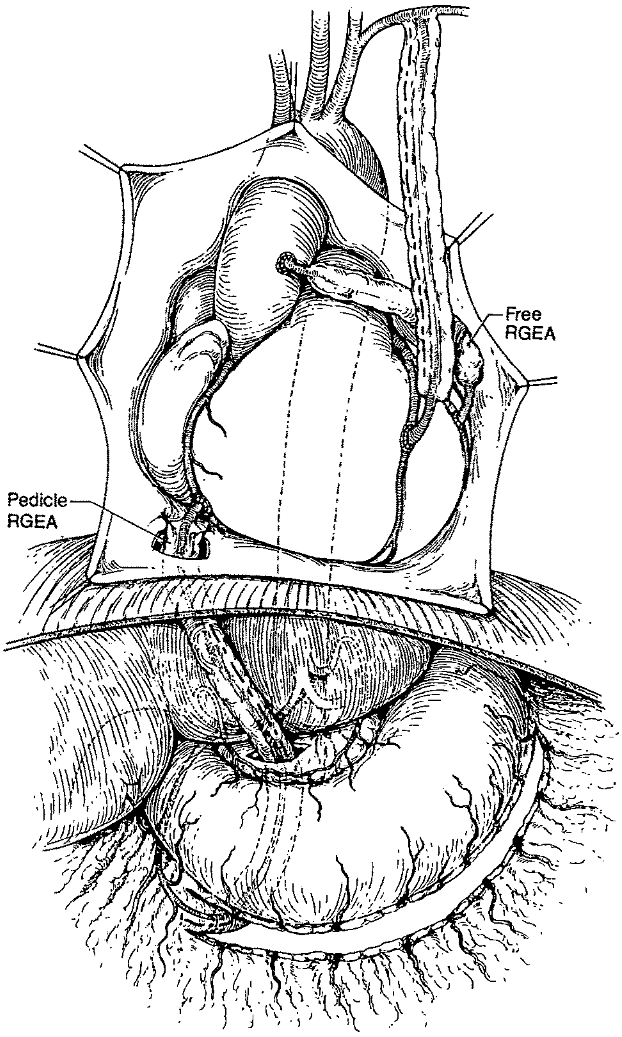

Fig 4. Route of the pedicled right gastroepiploic artery (RGEA) graft to the right coronary artery. Note that the dissection is not carried proximally to the origin of the anterior superior pancreaticoduodenal artery. The graft is most often routed posterior to the stomach through the avascular space of the lesser omentum and thereafter over the left lobe of the liver. The location of its entrance into the pericardium through a 2-cm^2 window is determined by the coronary artery to be bypassed. When the RGEA has sufficient length, the distal 10 cm can be placed as a short free graft to use more arterial conduit.

Use of the RGEA graft represents a step forward in the increased complexity of CABG operations and is analogous to the time when surgeons were making the transition from easier saphenous vein grafting to the more technically demanding IMA grafts. Much remains to be learned concerning RGEA patency, adequacy of flow, technical tricks, and resistance to atherosclerosis when used as a free graft. It may be that when Dr Sterling Edwards performed the first RGEA coronary bypass in conjunction with bilateral IMA bypass grafting in 1974, he was doing the operation that will offer the best coronary artery bypass in terms of longevity.

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Myocardial Revascularization With Combined Arterial Grafts Utilizing the Internal Mammary and the Gastroepiploic Arteries

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Coronary artery bypass grafting with a combined arterial graft using both the internal mammary artery and the right gastroepiploic artery was performed in 22 patients during a 21-month period. There were 17 men and 5 women ranging in age from 34 to 73 years (mean age, 53.4 years). Three patients were having a reoperation, and 2 patients had no segment of long saphenous vein available. Twelve patients were less than 55 years old. The mean number of distal anastomoses including vein grafts was 3.2 and the mean number of arterial grafts was 2.5 per patient. The mean aortic cross-clamp time was 63.8 minutes and the mean cardiopulmonary bypass time was 116.7 minutes. There was 1 early and 1 late death. The other 20 patients are alive without angina. Studied within 3 postoperative months, graft patency was 95% (19/20) in internal mammary artery and 93% (14/15) in gastroepiploic artery grafts. It is concluded that the combined arterial graft can be used safely and effectively, and its application facilitates complete revascularization with more arterial and fewer vein grafts.

(Ann Thorac Surg 1989;47:712–5)

In the 20-year experience with coronary artery bypass grafting (CABG), several studies have demonstrated the superiority of the internal mammary artery (IMA) graft in terms of graft patency [1–4], reoperation rate [5], and longevity [6–8]. The right gastroepiploic artery (GEA), on the other hand, has but recently been recognized as a suitable arterial conduit for CABG [9–11]. This report describes our 2-year experience with a combined arterial graft using both the IMA and GEA to accomplish complete revascularization with or without vein grafts.

Material and Methods

Twenty-two patients underwent CABG with the combined arterial graft with or without saphenous vein grafts during the 21-month period October 1986 to July 1988 at Osaka Medical College Hospital (n = 21) and its affiliated hospital (n = 1). One of us (H.S.) did all the operations. There were 17 men and 5 women ranging in age from 34 to 73 years (mean age, 54.3 years). The candidates were relatively select patients; 3 required reoperation, 2 had inadequate saphenous veins because of severe varicosis, and 12 were less than 55 years old.

Preoperative coronary angiograms showed single-vessel disease in 1 patient, double-vessel disease in 3 patients, triple-vessel disease in 16 patients, and left main disease in 2 patients. Preoperative left ventricular ejection fraction ranged from 0.45 to 0.73 (mean ejection fraction, 0.58). A previous myocardial infarction was noted in 10 patients. Unstable angina was present in 3 patients, 1 of whom underwent an emergency operation. Percutaneous balloon angioplasty had been attempted without success in 3 patients before operation.

The technique of IMA and GEA dissection has been described previously [10, 12, 13]. The free flow of these two arteries was measured in 8 patients; in the other patients they were utilized without flow measurement because they appeared to have good flow. No arterial graft was discarded after the dissection. The anastomosis between the arterial graft and the coronary artery was performed with the continuous suture technique using 8-0 Prolene (Ethicon). All distal anastomoses were done first under cardioplegic arrest with moderate (25° to 28°C) hypothermia. The mean aortic cross-clamp time was 63.8 minutes (range, 23 to 100 minutes), and the mean cardiopulmonary bypass time was 116.7 minutes (range, 69 to 136 minutes).

The left IMA and the right GEA were used in all patients, and the right IMA was used in 10 patients. Bypass grafting with one IMA and the GEA was done in 11 patients (50%), both IMAs and the GEA in 10 patients (45%), and a sequential IMA graft and GEA graft in 1 patient (5%). In addition, a saphenous vein graft was used in 9 patients (41%). The mean number of distal anastomoses was 3.2 per patient (range, 2 to 5), and the mean number of arterial graft anastomoses was 2.5 per patient (range, 2 to 3).

The IMA was anastomosed to 21 anterior descending, one diagonal, and 11 circumflex coronary arteries, a total of 33 arteries. The GEA was anastomosed to one anterior descending, one diagonal, one circumflex, and 19 right coronary arteries, a total of 22 arteries. One GEA was used as a free graft to bypass the first diagonal branch in a

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Table 1. Graft Patency[a]

	Site of Anastomosis				
Graft	LAD	Dx	Cx	RCA	Total
IMA	13/13 (100)	1/1 (100)	5/6 (83)	0	19/20 (95)
GEA	1/1 (100)	1/1 (100)	0	12/13 (92)	14/15 (93)

[a] Numbers in parentheses are percentages.

Cx = circumflex artery; Dx = diagonal branch; GEA = gastroepiploic artery; IMA = internal mammary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery.

patient having reoperation; all other arterial grafts were utilized as the in situ graft. One left IMA was used as a sequential graft to bypass the diagonal and the anterior descending coronary arteries. In total, 55 coronary arteries were bypassed with arterial grafts in these 22 patients.

The mean follow-up was 7.6 months (range, 2 to 24 months). Postoperative angiography was performed in 15 patients within 3 months after CABG.

Results

One patient died in the early postoperative period. After triple CABG was completed in this 51-year-old man with severe triple-vessel disease, sudden ventricular distention and fibrillation occurred just before the sternum was closed. Because the distal right IMA, which was anastomosed to the left anterior descending coronary artery, was found to be collapsed, an additional saphenous vein graft was urgently anastomosed. With intraaortic balloon pump support, cardiac function was restored, and the patient was returned to the general ward 1 week later. However, he died suddenly on the 22nd postoperative day of late cardiac tamponade during hemodialysis for postoperative renal failure.

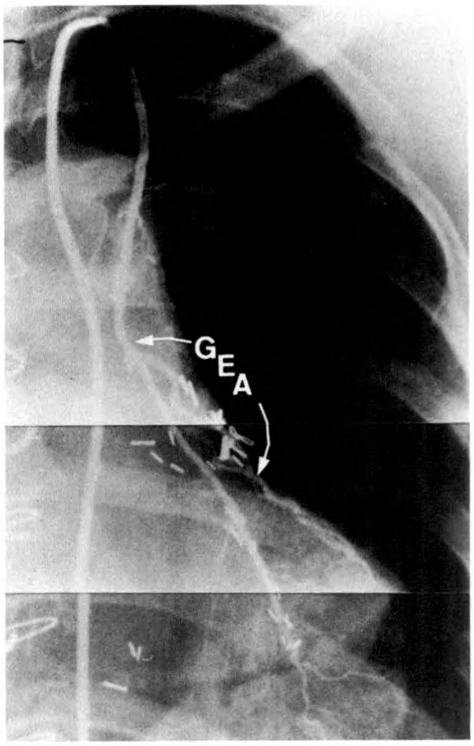


Fig 2. Angiogram of free gastroepiploic artery (GEA) *graft anastomosed to the first diagonal branch distally and to the left internal mammary artery graft proximally in a 57-year-old woman having reoperation.*

One patient with rectal bleeding died of stroke 2 months after CABG. The remaining 20 patients are alive

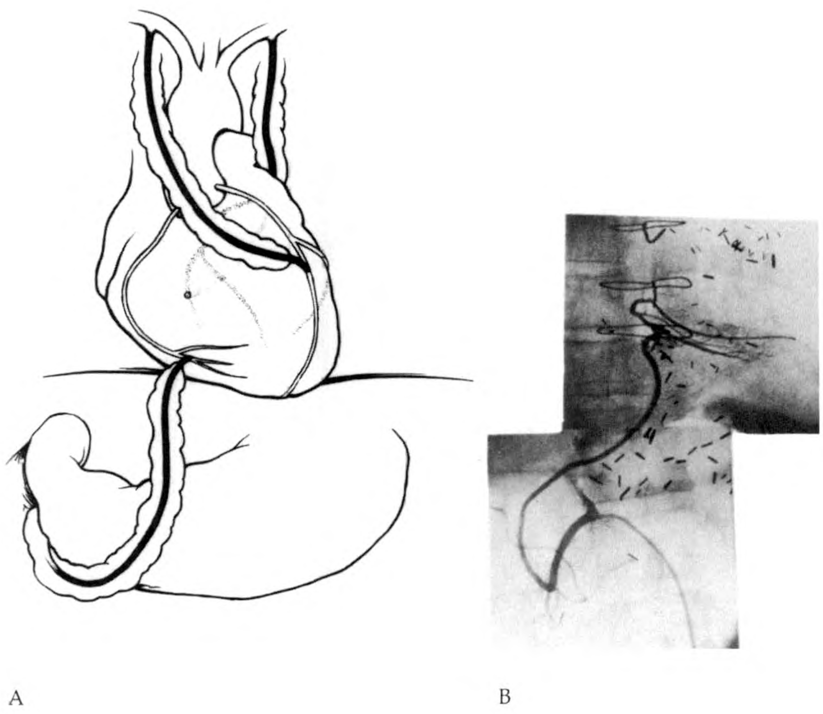


Fig 1. (A) Triple coronary artery bypass grafting utilizing combined arterial graft and (B) angiogram of right gastroepiploic artery graft in a 45-year-old man.

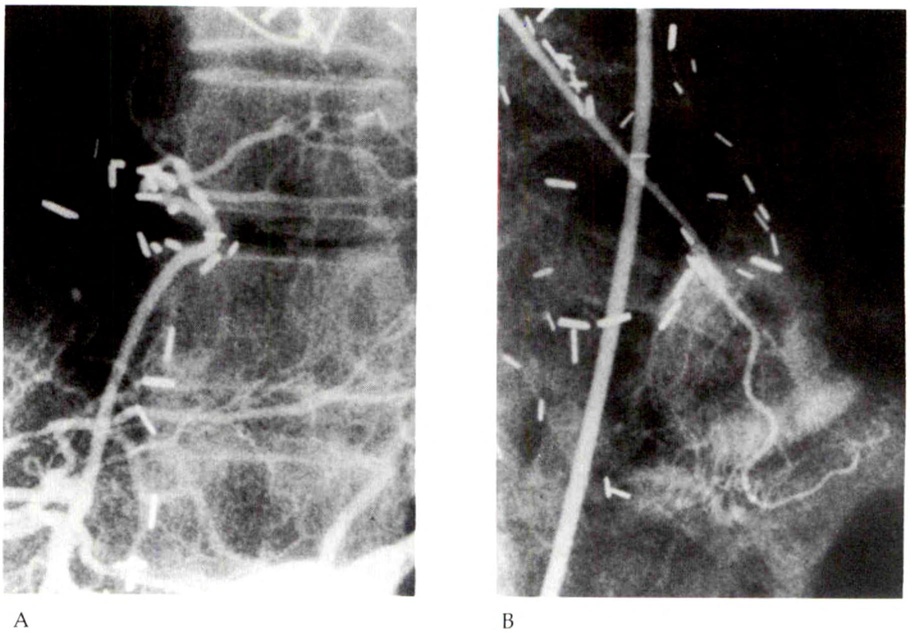

A B

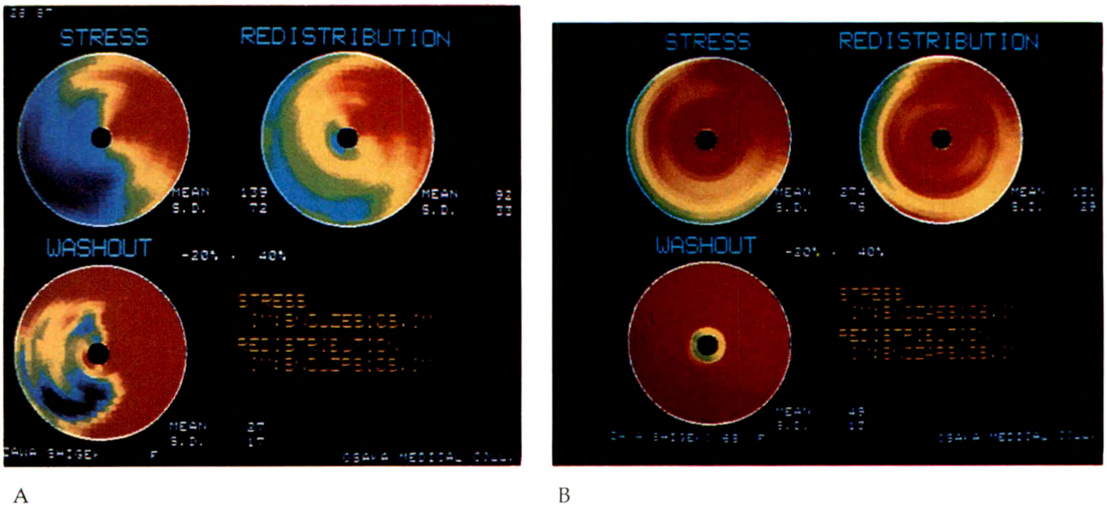
Fig 3. Angiogram of (A) right gastroepiploic artery anastomosed to the posterior descending coronary artery and (B) internal mammary artery anastomosed to the left anterior descending coronary artery in a 68-year-old woman.

and free from angina pectoris. A new Q wave was noted in 1 patient. Intraaortic balloon pumping was required in 3 patients, all of whom were weaned successfully.

The mean free flow of the IMA and the GEA was 83.0 mL/min (range, 50 to 120 mL/min) and 86.2 mL/min (range, 50 to 150 mL/min), respectively. The patency rate was 95% (19/20) in IMA and 93% (14/15) in GEA grafts (Table 1).

Figure 1 demonstrates triple CABG and an angiogram of a GEA graft anastomosed to the right coronary artery. The angiographic feature of the free GEA graft, anastomosed to the first diagonal branch distally and to the left IMA graft proximally, is shown in Figure 2. Figure 3 shows postoperative angiograms of a 68-year-old woman. The anterior descending and the posterior descending coronary arteries were bypassed with an IMA graft and a GEA graft, respectively. Preoperative and postoperative stress scintiscans of this patient are displayed in Figure 4. The preoperative scans showed an exercise-induced perfusion deficit with redistribution in the late image. This exercise-induced myocardial ischemia was not seen in the postoperative scans. Improved thallium washout was obvious in the anterior and inferior walls of the left ventricle after CABG.

Gastric bleeding from an ulcer at the lesser curvature of the stomach was noted in 1 patient on the third postoperative day, and was considered to be not related to GEA division. Gastrofiberscopic examination of 10 patients after CABG revealed no abnormalities in the mucosa of the greater curvature of the stomach. Mediastinitis oc-



A B

*Fig 4. Stress myocardial thallium scintigram (A) before and (B) after coronary artery bypass grafting with combined arterial grafts shown in Figure 3. Preoperative scintiscans showed stress-induced perfusion deficit (*blue color*) in the anteroseptal (◐) and inferior (◒) walls of the left ventricle. Restored normal perfusion (*red color*) was evident in postoperative scintiscans. Improved thallium washout was obvious.*

curred in 1 patient and was successfully treated by debridement and pectoral muscle flap implantation. Three patients were operated on without the requirement for blood transfusion.

Comment

Several investigations [1–8] have demonstrated the superiority of the IMA as the graft of choice in CABG procedures. However, it is not always possible to perform multiple bypass procedures with only the two IMAs, especially when they are small and short or one has already been used.

To find a new arterial graft, we [10] studied the GEA by celiac angiography and histological examination. Its successful clinical application has recently been reported by us [10] and by Pym [9], Lytle [11], and their associates. Historically, GEA implantation with a modified Vineberg procedure was reported by Bailey and co-workers [14] in 1966, and GEA graft patency was documented by Hirose and colleagues [15] in 1969. The GEA has also been reported to have less atherosclerotic changes, a finding of Larsen and associates [16] in pathological studies. Its similarity in size to the coronary artery and the technical feasibility of an in situ graft are major advantages to the GEA. Although the technique of using the splenic artery for CABG has been reported [17], splenectomy is necessary for this procedure. The dissection and division of the GEA, however, does not compromise the host organ. Because the distal right coronary artery, particularly the posterior descending coronary artery, is the nearest site to the in situ GEA graft, we preferentially perform a GEA–right coronary artery anastomosis instead of using the right IMA, which is the most distant from the posterior descending artery.

We do not think that routine preoperative celiac angiography is necessary in most patients because the risk of finding a GEA that is too small to use is only 5% [10]. Also, the quality of the GEA can be easily evaluated by palpation through the laparotomy at the time of CABG. We were able to use all the right GEAs in this series.

Concern has been expressed about upper abdominal operations after in situ GEA grafting. To date, no optimal procedure for such a situation has been established. Conversion from an in situ graft to a free graft seems to be the procedure of choice if the proximal site of the GEA graft has to be involved in the abdominal operation.

The flow capacity of the GEA is another important question to be answered. Postoperative exercise myocardial scintigraphy demonstrated absence of exercise-induced myocardial ischemia and marked improvement in the thallium 201 washout rate after combined arterial grafting, as reported by our group [18]. As shown in Figure 4, an adequate GEA flow to the ischemic myocardium is obvious.

The final important issue concerns the long-term patency of the GEA graft. This will be resolved in the future.

Even with these concerns still unanswered, we believe the GEA is a promising conduit. The indications for the procedure described here will be expanded with time and experience. The combined arterial graft utilizing the IMA and GEA can facilitate complete revascularization by arterial grafts safely and effectively.

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Right Gastroepiploic Artery as a Coronary Bypass Graft

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Between November 1987 and April 1988, the right gastroepiploic artery (GEA) was used as a coronary artery bypass graft in 11 patients, 9 men and 2 women. In 1 of them, the GEA was used because no veins were available; in the others, the GEA was used to avoid the use of vein grafts. The GEA was anastomosed to the right coronary artery in all patients, and internal mammary artery grafts were used to bypass the left anterior descending and circumflex coronary arteries. All patients survived the operation. There were no early and, to date, there have been no late complications of the abdominal component of the operation. Postoperative coronary angiography showed a patent right GEA in 9 patients (82%). In 1 patient the GEA was occluded, probably because of an enlarged liver. If the long-term patency of right GEA grafts is similar to that of internal mammary artery grafts, wider use of this viable graft is indicated.

(Ann Thorac Surg 1989;47:716–9)

The great saphenous vein has been routinely used as a bypass graft in coronary bypass procedures. However, degenerative changes developing over some years have caused several failures [1]. As the patency of internal mammary artery (IMA) grafts has been better, their use is currently widely recommended [2, 3]. However, in triple-vessel disease revascularization of the whole myocardium is, in practice, difficult, although not impossible, with both IMAs. Hence, the need for additional arterial grafts is evident.

In earlier years, a free radial artery graft was used as a bypass graft, but the results were disappointing [4]. The splenic artery was used by some, though there are difficulties in harvesting and degenerative changes have been observed in this graft [5].

A new arterial bypass graft, the right gastroepiploic artery (GEA), seems very promising [6–8]. Here we report our first experience with this graft in 11 patients.

Material and Methods

Patient Population

Between March 1987 and April 1988, the right GEA was used as a coronary artery bypass graft in 11 patients, 9 men and 2 women. Their mean age was 53 years (range, 31 to 67 years). All patients had a family history of coronary artery disease, 4 patients were hyperlipemic, and 2 patients had diabetes. Nine patients had had a previous myocardial infarction. In 1 patient, no vein grafts were available, and in the other 10, the GEA was used to avoid the use of a vein graft.

All patients had triple-vessel disease and disabling angina refractory to medical treatment. All but 1 patient were preoperatively in New York Heart Association functional class III or IV (Fig 1). The mean ejection fraction measured at left ventricular cineangiography was 58% (range, 45% to 85%); in 4 patients, the left ventricular ejection fraction was less than 50%.

The right GEA was used to bypass the right coronary artery in all patients, and both IMAs were used to bypass the left anterior descending and circumflex coronary arteries. In 3 patients, a saphenous vein graft was also used. A bifurcated right IMA was used in 2 patients, a bifurcated left IMA was used in 2, and a sequential left IMA graft was used in 1 patient (Table 1). There were 3.7 anastomoses per patient (range, 3 to 5), and 3.5 anastomoses were constructed with arterial grafts.

Follow-up examination was done 3 to 5 months after discharge. Multislice diagrams of gated Spect thallium 201 myocardial perfusion studies were obtained from all 11 patients using Elscint Apex 415 ECT equipment. Imaging was acquired by a 180 degree rotation using a Spect single-head system starting five minutes after injection of 2 mCi of thallium 201 chloride at peak exercise. The redistribution image was obtained three hours later. Thirty views were obtained at 6-degree intervals for 40 minutes using a low-energy all-purpose collimator (Elscint APC-3). Routine uniformity and radius-of-rotation checks were performed. Data were acquired using a 64 × 64 matrix. The pixel size was 0.6 cm with a similar thickness.

Image reconstruction was generated by a minicomputer (Apex F1, Elscint). For reconstruction, only the early systolic and late diastolic phases of the gated frames were used to reduce motion artifact. Images were displayed using a segmental color scale for semiquantification. Each separate color indicated a 10% change in counts. The images were normalized so that the maximum pixel was at the point of 100%. Also, washout analysis of thallium

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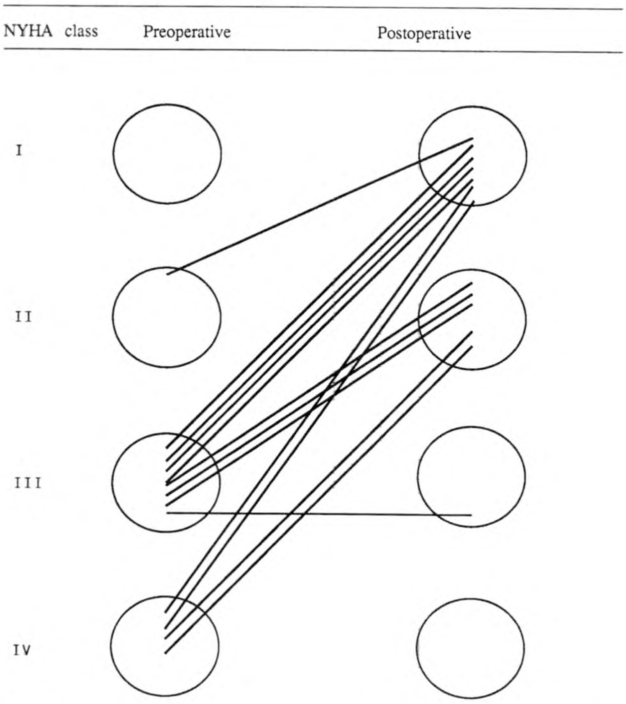

Fig 1. Preoperative and postoperative New York Heart Association (NYHA) functional class of patients undergoing coronary artery bypass grafting with the right gastroepiploic artery.

201 based on comparison of the immediate postexercise and redistribution images was performed.

In addition, coronary angiography combined with celiac axis angiography was performed.

Operative Technique

Table 1. Grafts Used for Coronary Anastomoses

		Coronary Artery Grafted					
Patient No.	Sex	LAD	Left Diagonal	First OM	Second OM	Third OM	RCA
1	M	RIMA	SVG	. . .	LIMA	. . .	RGEA
2	M	BRIMA	BRIMA	LIMA	. . .	. . .	RGEA
3	F	RIMA	. . .	. . .	LIMA	. . .	RGEA
4	M	RIMA	. . .	. . .	BLIMA	BLIMA	RGEA
5	M	RIMA	BLIMA	BLIMA	SVG	. . .	RGEA
6	M	RIMA	. . .	. . .	LIMA	. . .	RGEA
7	M	BRIMA	BRIMA	. . .	LIMA	. . .	RGEA
8	M	RIMA	. . .	SVG	LIMA	. . .	RGEA
9	M	RIMA	. . .	. . .	LIMA	. . .	RGEA
10	F	RIMA	. . .	. . .	LIMA	. . .	RGEA
11	M	RIMA	SLIMA	SLIMA	. . .	. . .	RGEA

BLIMA = bifurcated LIMA; BRIMA = bifurcated RIMA; LAD = left anterior descending coronary artery; LIMA = left internal mammary artery; OM = obtuse marginal artery; RCA = right coronary artery; RGEA = right gastroepiploic artery; RIMA = right internal mammary artery; SLIMA = sequential left internal mammary artery; SVG = saphenous vein graft.

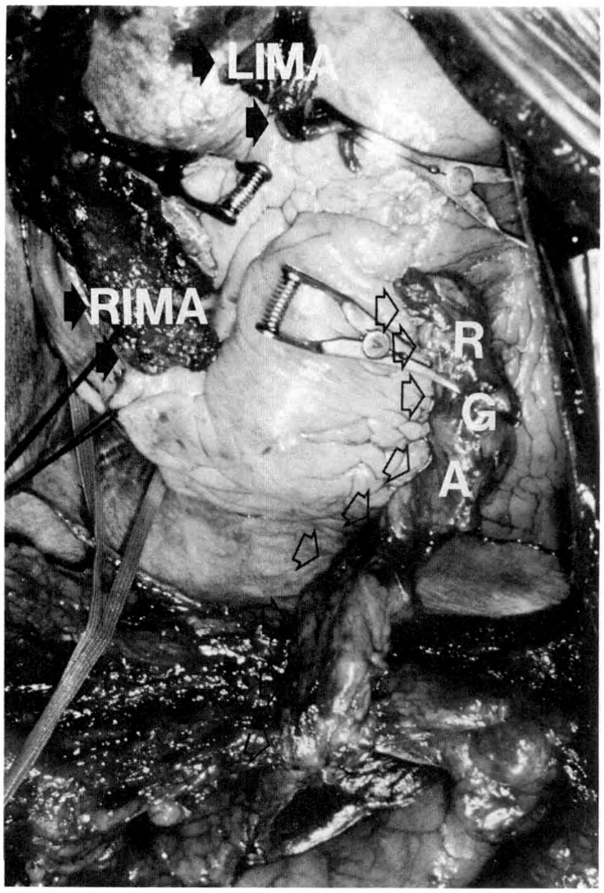

Fig 2. Intraoperative photograph demonstrates sufficient length of a right gastroepiploic artery (RGA) graft (clear arrows). *Left (LIMA) and right internal mammary artery (RIMA) grafts* (black arrows) *also are shown.*

A median sternotomy incision was extended to below the midpoint between the xiphoid process and the umbilicus. Both mammary arteries including the terminal bifurcation were dissected with electrocautery and metallic hemostatic clips. The right GEA was detached from the greater curvature of the stomach to the junction with the left GEA using 3-0 polyglycolic ligatures. The artery was left in the pedicle to preserve its blood supply.

After systemic heparinization, the three arterial grafts were transected and papaverine hydrochloride was injected into all of them. The time needed for preparation of the three arterial grafts was, on average, 86 minutes (range, 78 to 120 minutes). Figure 2 shows the operative area after preparation of all three arterial grafts. In 4 patients, the free flow of the grafts was measured. For left IMA grafts it was, on average, 90 mL/min (range, 80 to 100 mL/min); for right IMA grafts, 88 mL/min (range, 72 to 110 mL/min); and for GEA grafts, 85 mL/min (range, 60 to 140 mL/min). In the other 7 patients, the diameter and free flow of the GEA were considered clearly sufficient. Preoperative celiac axis angiography was not performed.

In 9 patients, the GEA was placed anteriorly and in 2, behind the pylorus. The route was selected according to the anatomical situation and the site of the coronary anastomosis to avoid kinking. In 10 patients, the graft was brought into the pericardial cavity through a hole in the diaphragm, and in 1 patient, a slit was made because of a voluminous pedicle.

The standard technique of cardiopulmonary bypass with a bubble oxygenator was used. Mild general hypothermia with cold chemical cardioplegia and topical cooling was used for myocardial protection. Coronary anastomoses were performed with 7-0 or 8-0 continuous polypropylene sutures, in general. All GEA grafts were sutured with 8-0 polypropylene sutures. All patients received prophylactic antibiotic treatment for two days, beginning at induction of anesthesia. Time of operation averaged 280 minutes (range, 205 to 330 minutes); perfusion time, 108 minutes (range, 83 to 127 minutes); and aortic cross-clamp time, 63 minutes (range, 48 to 79 minutes).

Results

All patients survived the operation, but major postoperative complications developed in 4 patients. In 1 patient, hemiplegia on the left side developed on the first postoperative day after initial recovery. He had had a previous transient ischemic attack 6 months earlier on the same side. Two patients were reoperated on because of bleeding from distal side branches of the right IMA. In 1 patient with diabetes, mediastinitis developed on the tenth postoperative day. The patient was successfully treated with sternal refixation and mediastinal lavage, and she had no angina at follow-up.

At the follow-up examination 3 to 5 months postoperatively, all but 1 patient showed clinical improvement (see Fig 1). The coronary angiogram showed a patent GEA in 9 patients (82%) (Fig 3). In 2 patients, the GEA could not be visualized. In 1 of them, the GEA was occluded, probably because of an enlarged liver. This woman had had mitral insufficiency preoperatively, which worsened postoperatively. In the other patient, the right coronary artery was of poor quality, which predisposed to occlusion. Thallium myocardial perfusion studies showed no signs of ischemia in the area perfused by the GEA in 9 patients. In 2 patients, signs of ischemia were seen; these were the patients in whom the GEA could not be seen on angiography.

Comment

The right GEA is suitable as a coronary bypass graft for several reasons. Harvesting is very easy and seems to be associated with no or very few early or late complications. In our series, no GEA-related complications occurred; a similar initial experience has been reported [6]. Although in the present series the GEA was used to bypass only the right coronary artery, our later experience with 22 patients to date also includes GEA anastomoses to the left anterior descending coronary artery. The free flow of the GEA in our patients was similar to that of the IMAs, and as an arterial graft, it is probably capable of adapting to the needs of a grafted coronary artery.

The indications for use of the right GEA are numerous. There is a substantial group of patients in whom no suitable vein grafts are available because of poor quality or earlier removal, as in the case of patients having a redo coronary bypass procedure. In some patients, the ascending aorta is so severely calcified that the implantation of vein grafts is associated with major complications. With the help of IMAs and the right GEA, revascularization of the whole myocardium is possible without vein grafts and without an aortic anastomosis.

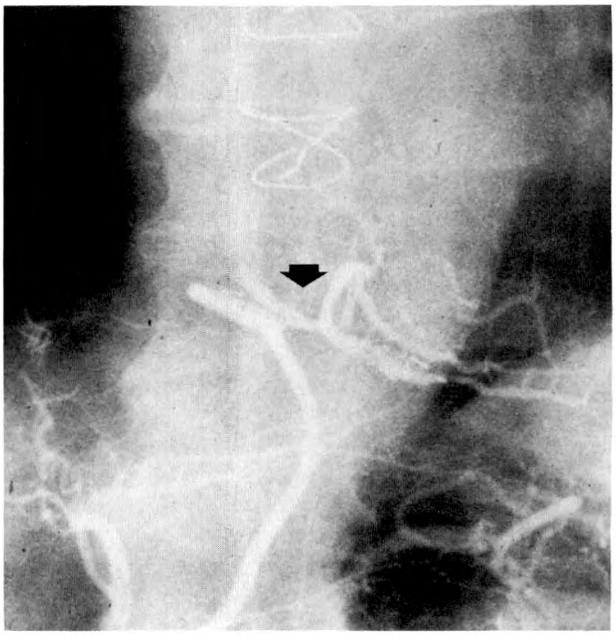

Fig 3. Postoperative angiogram of the celiac axis showing a patent and well-functioning right gastroepiploic artery graft to the atherosclerotic right coronary artery. The site of anastomosis is indicated by the black arrow.

One advantage of a right GEA graft is the lack of interference with the sternal blood supply, which is impaired when both IMAs are used [9]. In patients with a compromised host defense, this may be important for sternal wound healing. Whether the GEA influences long-term results of coronary artery bypass grafting can be answered only after several years.

There may be some relative or absolute contraindications to use of the right GEA. We have not used this artery in patients with a previous laparotomy because the dissection can be difficult and associated with postoperative bleeding. Also, severe obesity may be a relative contraindication. A history of abdominal illness probably necessitating a future laparotomy is another relative contraindication. When a secondary laparotomy is indicated, knowledge of a previous right GEA–coronary artery anastomosis is important to prevent operative injury. The positioning of the GEA behind the pylorus may be advantageous to prevent injury during laparotomy. It remains to be investigated whether a "free" right GEA graft is better at avoiding these difficulties. In the presence of hepatomegaly or if the length of the pedicle is questionable, use of the right GEA as a free graft is indicated.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the cardiothoracic operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1991 may begin the recertification process in 1989. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1989. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Mitral Valve Replacement in the First 5 Years of Life

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Between 1976 and 1986, 19 children aged 1 month to 5 years underwent replacement of the mitral (systemic atrioventricular) valve. Indications for valve replacement included isolated congenital mitral stenosis (n = 2), valve dysfunction associated with a more complex procedure (n = 15), and failed valvuloplasty (n = 2). Seven different valve types were used; nine were mechanical valves and ten were bioprosthetic valves. There were 6 hospital deaths (32%; 70% confidence limits, 20% to 47%). Among the 13 survivors there were 3 late deaths at a mean of 14 months after operation. The late deaths were unrelated to valve malfunction. Thromboembolic events occurred in 2 patients, both with mechanical valves. One minor bleeding complication occurred among 10 patients on a regimen of Coumadin (crystalline warfarin sodium). Five patients, all with bioprostheses, required a second valve replacement. Indications for reoperation included prosthetic valve regurgitation (n = 1) and calcific stenosis (n = 4). No early or late deaths occurred after second valve replacement. Survival was 51% ± 12% (standard error) at 112 months after valve replacement. Analysis failed to identify age, weight, sex, previous operation, underlying cardiac lesion, or prosthesis size and type as significant risk factors for mortality. Mechanical valves had a lower reoperation rate compared with bioprostheses. These data suggest that although mitral valve replacement within the first 5 years of life is associated with a high operative and late mortality, satisfactory long-term palliation for many patients can be achieved. Mechanical valves are superior to bioprosthetic valves, and offer the best long-term results.

(Ann Thorac Surg 1989;47:720–4)

Among the wide variety of congenital heart lesions requiring operative correction, replacement of the mitral valve is seldom necessary. Valve conserving techniques are generally successful, and replacement is reserved for patients with severe valvular deficiency not amenable to repair. The choice of the ideal valve substitute remains controversial [1–8]. Experience with glutaraldehyde-treated porcine heterografts in children has shown early degenerative calcification resulting in an unacceptable rate of valve failure [7, 9–12]. Mechanical valves usually require anticoagulation with warfarin derivatives, which subjects active, growing children to the risks of bleeding [13]. Although some reports [1, 14] have suggested that antiplatelet therapy is adequate to prevent thromboembolism in children with mechanical prostheses, the adequacy of such treatment in preventing thromboembolic events in children with mechanical valves has recently been questioned [15].

Experience with mitral valve replacement in the pediatric age group has been limited, especially in infants and children within the first few years of life. This select group of patients poses unique problems associated with limited valve selection, obstructive hemodynamics of small prostheses, rapid patient growth, and difficulty with anticoagulation [3, 16–20]. This report reviews our 10-year experience with mitral valve replacement in 19 children within the first 5 years of life.

Material and Methods

Nineteen consecutive patients (9 male and 10 female) within the first 5 years of life underwent replacement of the mitral valve at C.S. Mott Children's Hospital of The University of Michigan or at The State University of New York Health Science Center at Syracuse between July 1976 and July 1986. All clinical records were reviewed, and follow-up information was complete to June 1987. Patient age at the time of initial valve replacement ranged from 1 month to 5 years with a mean of 31 months (Fig 1). Weight ranged from 3.0 to 17.0 kg with a mean of 9.3 kg (Fig 2). Follow-up information was complete for all patients and ranged from 11 to 112 months after valve replacement (mean follow-up, 42 months).

These 19 patients underwent a total of 24 valve replacements. The valve was a morphological mitral valve in 11 patients, a left-sided component of a common atrioventricular valve in 6 patients, and a morphological tricuspid valve in 1 patient each with transposition of the great arteries and atrioventricular discordance. Indications for valve replacement included stenosis in 5 patients (2 with isolated congenital stenosis and 3 with Shone's syndrome), combined congenital stenosis and regurgitation in 3 patients, and regurgitation in 11 patients (2 with isolated congenital regurgitation, 6 with atrioventricular septal defects, and 3 with other complex lesions) (Table 1).

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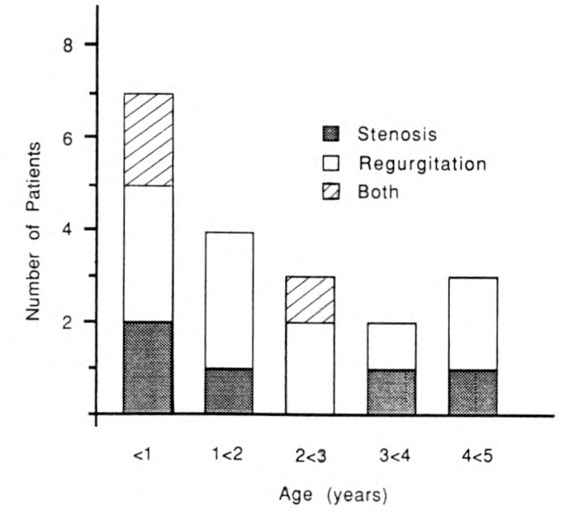

Fig 1. Age distribution of patients undergoing mitral valve replacement (data for initial valve replacement only).

Table 1. Diagnoses in 19 Patients Undergoing Mitral Valve Replacement

Diagnosis	No. of Patients[a]
Isolated congenital mitral stenosis	2 (1)
Isolated congenital mitral regurgitation	2
Combined mitral stenosis and regurgitation	3
Atrioventricular septal defect	6 (2)
Shone's syndrome	3 (2)
Transposition of great arteries, ventricular septal defect, previous Mustard operation	1
Atrioventricular discordance	1
Truncus arteriosus	1 (1)
Total	19 (6)

[a] Number in parentheses represent perioperative deaths.

Twenty-three operations had been performed prior to valve replacement (Table 2), and 11 patients underwent additional procedures at the time of valve replacement (Table 3). A second valve replacement was performed in 5 patients for prosthetic valve regurgitation (n = 1) or bioprosthetic stenosis (n = 4).

Cardiopulmonary bypass and systemic hypothermia (18° to 25°C) were used for all procedures. Myocardial protection was provided with cold crystalloid or blood cardioplegia and topical hypothermia. The choice of valve varied greatly over the years of study, and was based on patient age, annulus size, and left ventricular cavity size (Table 4). Since 1980, mechanical prostheses generally have been preferred.

Patients receiving a bioprosthesis did not routinely receive anticoagulation or antiplatelet therapy postoperatively. All patients with Starr-Edwards mechanical valves were anticoagulated with Coumadin (crystalline warfarin sodium). Among the remaining patients, initial drug therapy consisted of aspirin and Persantine (dipyridamole) in 6 patients and Coumadin in 4 patients.

The charts of all 19 patients were reviewed. Besides death, notation was made if a patient sustained a morbid event, defined as bleeding, thromboembolism, infection, or need for further cardiac valve operation.

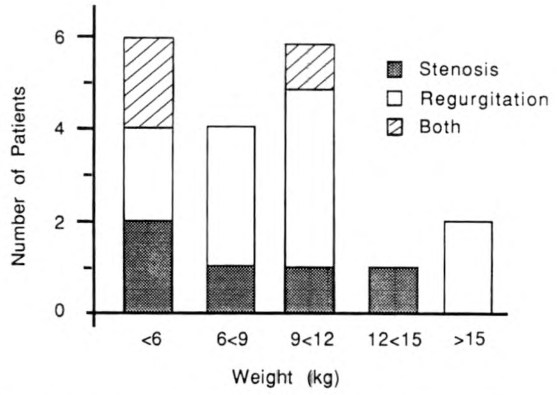

Fig 2. Weight distribution of patients undergoing mitral valve replacement (data for initial valve replacement only).

Kaplan-Meier analysis was used to study patient and event-free survival status. The following data were examined as predictors for early and late mortality and morbidity: age less than 1 year, weight less than 12 kg, weight less than 10 kg, sex, underlying cardiac lesions (stenosis, regurgitation, both), prosthesis size and type, and previous or simultaneous operation. Fisher's exact test (for the categorical predictors) and analysis of variance and Student's t test (for measured predictors) were used to determine statistical significance of data.

Results

Hospital (30-day) mortality was 32% (70% confidence limits, 20% to 47%), 6 of 19 patients. Three patients died

Table 2. Prior Operations in Patients Undergoing Valve Replacement[a]

Procedure	No. of Patients
Isolated valvuloplasty	3
Aortic and mitral valvuloplasty, resection of subaortic stenosis	1
Repair of aortic coarctation	3
Repair of atrioventricular septal defect	7
Closure of ventricular septal defect, mitral valvuloplasty	2
Closure of atrial septal defect	1
Pulmonary artery banding	2
Atrial septectomy	1
Mustard procedure	1
Ligation of patent ductus arteriosus	2
Total	23

[a] Some patients had two or more prior operations.

Table 3. Additional Procedures in Patients Undergoing Valve Replacement

Procedure	No. of Patients[a]
Repair of truncus arteriosus	1 (1)
Repair of anomalous left coronary artery	1
Repair of baffle leak (Mustard)	1
Closure of atrial septal defect	1
Repair of atrioventricular septal defect	2 (1)
Repair of atrioventricular septal defect, right atrial–right ventricular conduit	1
Closure of VSD, resection of subaortic stenosis, right ventricular outflow tract patch	1
Repair of coarctation, closure of VSD	1 (1)
Left ventricular–apical aortic conduit	1 (1)
Balloon dilation of mitral stenosis	1 (1)
Total	11 (5)

[a] Numbers in parentheses represent perioperative deaths.

VSD = ventricular septal defect.

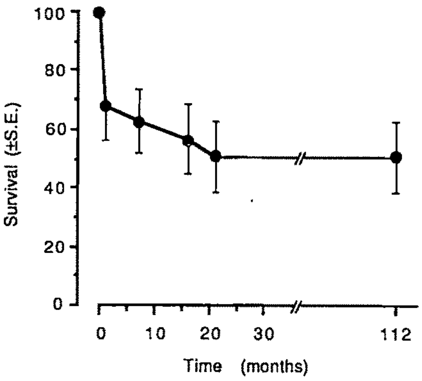

Fig 3. Actuarial survival for 19 patients undergoing mitral valve replacement. (S.E. = *standard error.)*

intraoperatively of severe left ventricular dysfunction and the inability to be weaned from cardiopulmonary bypass. Two of these patients were found at autopsy to have previously unsuspected hypoplasia (n = 1) or atresia (n = 1) of the left main coronary artery. The third intraoperative death occurred in a patient in whom severe acute mitral regurgitation developed two hours after repair of an atrioventricular septal defect. This patient sustained cardiac arrest before the institution of cardiopulmonary bypass and was unable to be weaned from bypass after valve replacement.

Two patients with Shone's syndrome died. Profound low cardiac output developed in both, and they died within hours of operation. One patient with congenital mitral stenosis who underwent balloon valvuloplasty died. Balloon valvuloplasty resulted in severe mitral regurgitation and necessitated valve replacement. The patient died on the first postoperative day of ventricular failure associated with uncontrollable tachyarrhythmias.

Table 4. Prosthetic Valve Used for Mitral Valve Replacement

Type of Valve	Initial Replacement[a]	Second Replacement
Bioprosthesis		
Carpentier-Edwards	1	0
Hancock	5 (2)	0
Ionescu-Shiley	4 (1)	0
Mechanical Prosthesis		
Björk-Shiley	1 (1)	0
Lillehei-Kaster	0	1
Omniscience	2 (1)	0
St. Jude	5 (1)	1
Starr-Edwards	1	3
Total	19 (6)	5

[a] Numbers in parentheses represent perioperative deaths.

There were 3 late deaths (23%) among the 13 patients surviving initial valve replacement. The mean interval between operation and late death was 14 months (range, 6 to 21 months). One patient died of unknown causes 16 months after valve replacement. Autopsy revealed a normal prosthetic valve and no associated thrombus. One patient died 21 months after operation of aspiration pneumonia associated with acute epiglottitis. In another patient, right ventricular failure and pneumonia developed, and the patient died 6 months postoperatively. Echocardiography revealed a properly functioning prosthetic valve just before death. Survival for the entire patient group is shown in Figure 3.

Thromboembolic events occurred in 2 of the 13 survivors. One 3-year-old patient had a Starr-Edwards valve and was anticoagulated with Coumadin when she sustained a cerebrovascular accident 10 months after operation. It resolved completely. Antiplatelet therapy with Persantine was added to the Coumadin therapy. The second patient was a 2-month-old infant with an Omniscience valve who was receiving aspirin and Persantine. A cerebrovascular accident occurred 6 months after valve replacement. Anticoagulation with Coumadin was added. Neither patient has experienced additional embolic events. One of 10 patients receiving Coumadin had a small hematoma of the right shoulder after a fall. No other bleeding complications occurred among these patients. Endocarditis did not develop in any patient in this series during the study period. All patients who survived valve replacement had marked clinical improvement and relief of congestive heart failure.

Severe bioprosthetic stenosis necessitating a second valve replacement occurred in 4 of 10 patients from 17 to 47 months (mean, 34 months) after the initial replacement. A mechanical prosthetic valve was used in each patient. One additional patient required reoperation nine days after insertion of an Ionescu-Shiley prosthesis because of regurgitation caused by a suture looped around a valve strut. The age, weight, body surface area, and prosthesis size at the initial and second valve replacements are shown in Table 5. Second valve replacement was associated with no mortality.

Table 5. Data on 5 Patients Requiring Second Valve Replacement

	Age (mo)		Weight (kg)		Body Surface Area (m^2)		Prosthesis Size (mm)	
No. Patient	First OP	Second OP	First OP	Second OP	First OP	Second OP	First OP	Second OP
1	66	109	17	27	0.70	1.00	23	25
2	41	58	13	14	0.56	0.58	17	21
3	18	65	9	16	0.41	0.65	23	22
4	34	34.3	10	10	0.44	0.44	21	22
5	13	44	8	11	0.39	0.50	19	22

OP = operation.

Event-free survival for the entire series was 47% ± 13% at 54 months (Fig 4), slightly less than patient survival.

Statistical analysis of the data failed to identify age, weight, sex, previous or simultaneous operation, underlying cardiac lesion, prosthesis size, or type of valve as a risk factor for early or late death. A significantly higher morbidity was associated with simultaneous operation, however ($p = 0.04$).

Comment

This study evaluates the results of mitral (systemic atrioventricular) valve replacement in children within the first 5 years of life. Previous reports [11, 21, 22] of valve replacement have usually included older children, often including them among the younger group. This series highlights several unique problems in the management of infants and small children.

Mitral valve replacement carries a substantial operative risk in young patients. Our operative mortality of 32% is similar to that reported by others (Table 6). Analysis of risk factors including age, weight, sex, previous or simultaneous operation, and prosthesis type or size failed to demonstrate any significant predictors of early or late death. Valve replacement for stenosis (either isolated or associated with Shone's syndrome) was, however, associated with a higher operative mortality than replacement for regurgitation (60% versus 27%; $p = 0.24$). This may have been secondary to the smaller prostheses required for the patients with isolated mitral stenosis ($p = 0.08$).

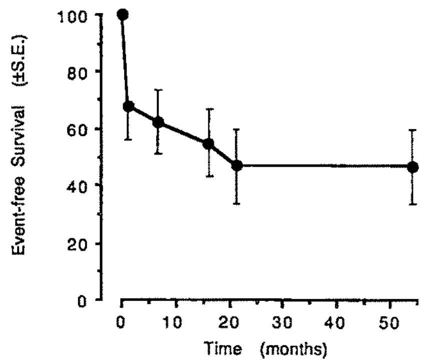

Fig 4. Event-free survival for 19 patients undergoing mitral valve replacement. (S.E. = *standard error.)*

The choice of prosthetic valve type remains controversial. Early in this series, bioprosthetic valves were predominantly used to avoid anticoagulation in young children. However, our experience as well as that of others [4, 12, 29] clearly demonstrates the high probability of early calcific stenosis and subsequent need for early prosthesis replacement when bioprosthetic valves are used. The advantages of mechanical valves include better hemodynamic flow characteristics in small sizes, low profile with less left ventricular outflow tract obstruction, and improved durability. Currently, we prefer the St. Jude Medical prosthesis because of its favorable hemodynamic characteristics and low thromboembolic complication rate [1, 14].

The hazards of managing anticoagulation therapy in young children must be compared with the serious risk of valve thrombosis or thromboembolism. A number of our patients with mechanical valves were treated with antiplatelet drugs only. However, isolated reports [15] question the safety of this approach in preventing thromboembolic events and recommend anticoagulation with Coumadin, even with the St. Jude valve. We currently individualize the management of these patients but favor the use of Coumadin. Anticoagulation in these patients has generally been safe and uncomplicated.

Table 6. Published Series on Mitral Valve Replacement in Patients Less Than 5 Years of Age

Reference	No. Of Patients	Deaths	Mortality (%)
Borkon et al [1]	7	2	29
Gardner et al [3]	8	NA	NA
Human et al [4]	5	NA	NA
Milano et al [9]	21	NA	NA
Schaffer et al [23]	10	2	20
Spevak et al [24]	45	13	29
Schachner et al [25]	5	1	20
Duncan et al [26]	2	2	100
Galioto et al [27]	6	2	33
Sanders et al [28]	6	3	50
Zweng et al [this report]	19	6	32
Total			31

NA = not available.

The absence of prosthetic valve endocarditis in this series is unusual compared with other series of pediatric patients undergoing valve replacement [11]. This may be related to the relatively short follow-up for some of our patients. The use of small prosthetic valves in infants and small children will eventually necessitate replacement. Prosthetic valve replacement was not associated with any operative deaths in this series. Nudelman and colleagues [30] demonstrated that the annulus of the mitral valve will grow even when fixed to a prosthetic valve sewing ring, thereby permitting the use of a larger-sized valve at the time of prosthetic valve replacement. Our clinical experience supports these data.

The results of this series demonstrate that mitral valve replacement is associated with a substantial operative and late mortality in infants and young children within the first 5 years of life. The serious underlying condition of these patients, however, justifies this approach when valve-conserving procedures are unsuccessful. Mechanical prostheses appear superior to bioprostheses, and anticoagulation with Coumadin is preferred for all ages. When necessary, valve replacement can be performed safely and provide extended palliation for many patients. Nearly half of our patients remained well and free from major complications or reoperation more than 4 years after valve replacement.

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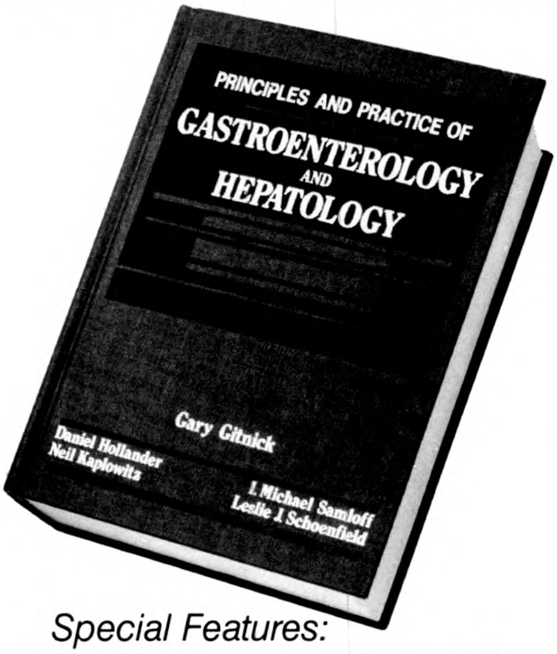

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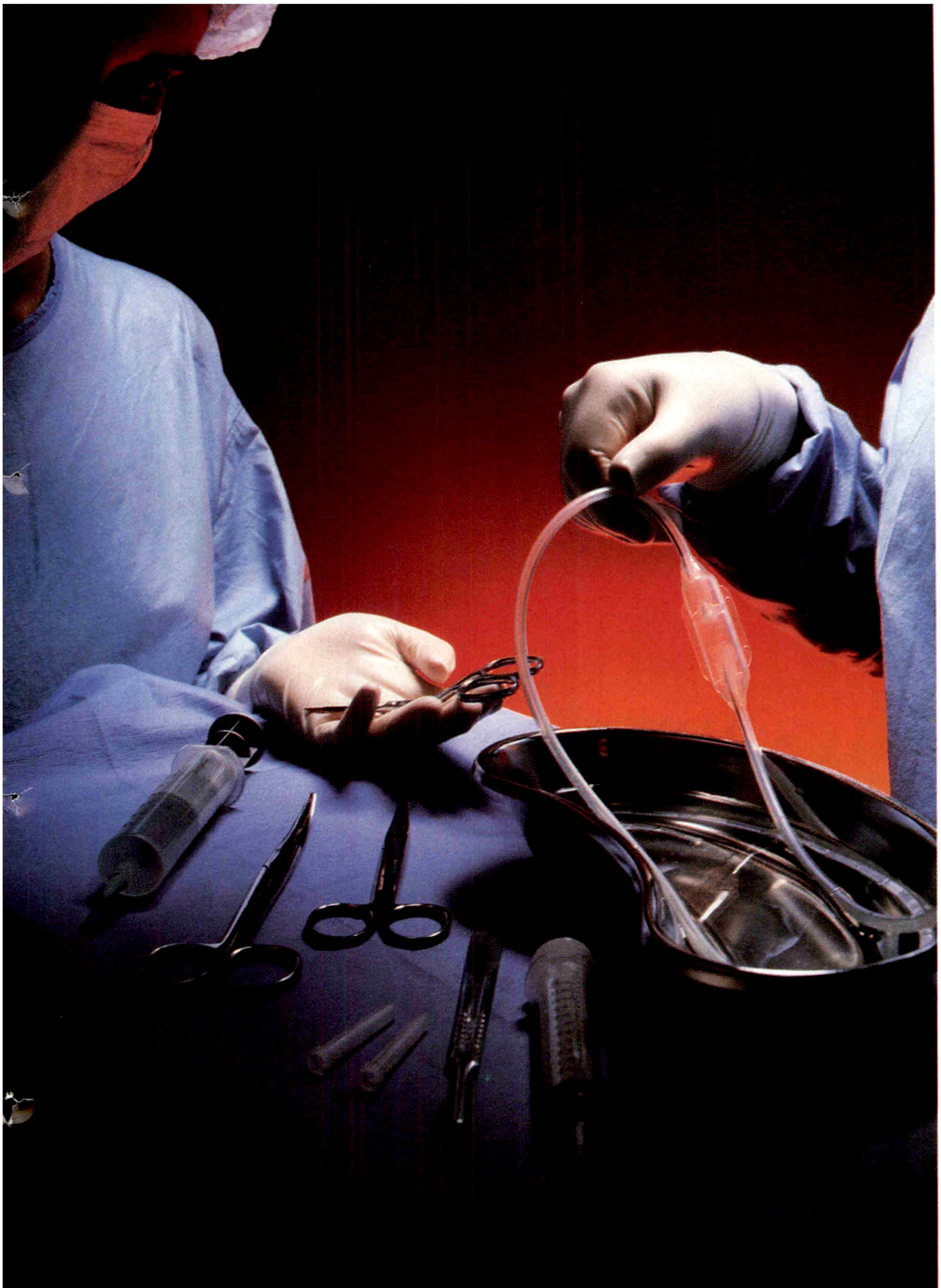

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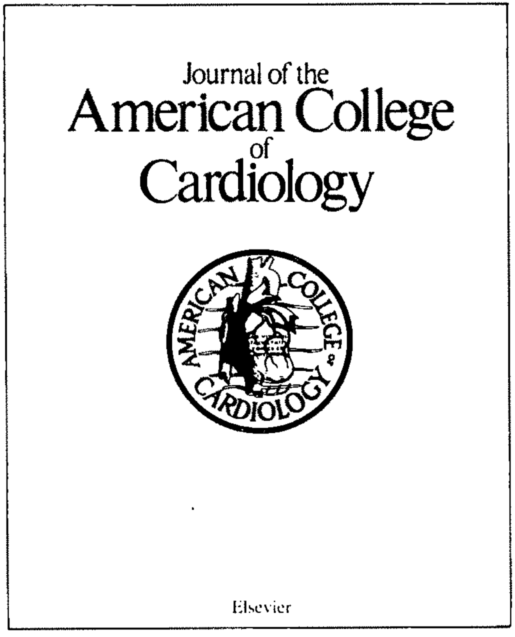

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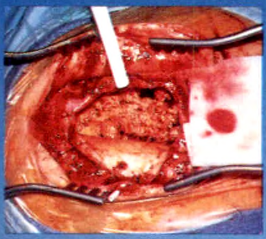

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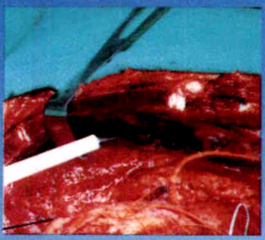

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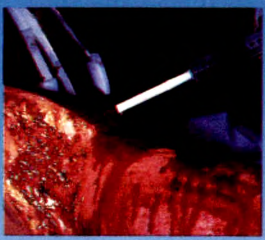

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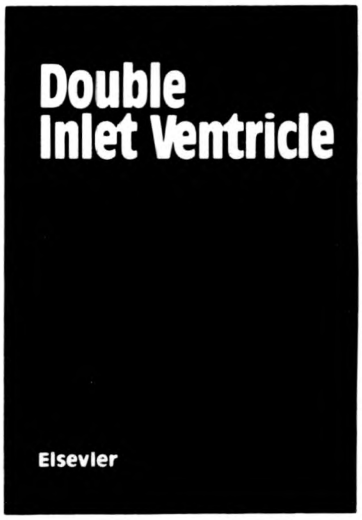

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Warm (30°C) blood cardioplegia (K = 22 mEq/L) with glutamate (26 mmol/L) as a reperfusate was compared with unmodified blood reperfusion after prolonged hypothermic storage of the isolated canine heart. After cardioplegic arrest, three groups of hearts (n = 5 each) were excised and stored at 2°C. In groups 1 and 2, reperfusion with unmodified blood was undertaken after six and 24 hours of storage, respectively, and in group 3, reperfusion with modified warm blood cardioplegia containing glutamate was administered after 24 hours of storage. After reperfusion, no significant difference in left ventricular developed pressure was noted between groups 1 (110 ± 15 mm Hg), 2 (127 ± 14 mm Hg), and 3 (98 ± 13 mm Hg). Similarly, no difference in maximum rate of rise of left ventricular pressure was noted between groups 1 (1,456 ± 171 mm Hg/s), 2 (1,905 ± 395 mm Hg/s), and 3 (1,450 ± 291 mm Hg/s). Group 3 (modified reperfusate) had improved diastolic compliance compared with group 2 (0.776 mm Hg/mL versus 1.395 mm Hg/mL; $p < 0.02$). We conclude that our modified reperfusate improves diastolic function after 24 hours of hypothermic storage, but does not result in improved systolic function.

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Since 1967, when the first human cardiac transplantation was performed, long-term preservation of the myocardium for subsequent transplantation has been a desirable goal. Although optimal methods of myocardial protection are not yet established, most research efforts have focused on either ischemic hypothermic storage [1–3] or continuous hypothermic perfusion [4–9]. Perfusion techniques are often complex and somewhat impractical for clinical use, and have been limited by the development of severe edema. Hypothermic storage methods, although simple and conducive to easy transport, have, to date, been limited clinically to less than four to six hours [10, 11].

Injury may be due to the effects of reperfusion after prolonged ischemia. Experimental and clinical studies by Buckberg and associates [12–14] have shown that after shorter periods of ischemia, the use of a warm modified reperfusate can reduce the reperfusion injury. Swanson and associates [15] have studied the effects of modified reperfusate after prolonged ischemia, and have had encouraging results. The present study was undertaken to evaluate the efficacy of a modified reperfusate with substrate enhancement on 24-hour hypothermic storage of the heart in a setting similar to clinical use.

Material and Methods

Three groups of mongrel canine hearts were excised after cardioplegic arrest and stored in Sacks II solution (a hyperkalemic, hyperosmotic intracellular solution) at 2°C for variable periods of time. The composition of the solution is as follows:

K = 126 mEq/L
Na = 14 mEq/L
Cl = 16 mEq/L
HCO_3 = 20 mEq/L
Mg = 16 mEq/L
PO_4 = 120 mEq/L
Mannitol = 37.5 g/L
Osmolality = 430 mosm/L
pH (4°C) = 7.0

Group 1 hearts (n = 5) were stored for six hours, and groups 2 and 3 hearts (n = 5 each) were stored for 24 hours.

Reperfusion was carried out using a support animal with blood supplied from the femoral artery to the aorta and returned to the vein of the support animal. Groups 1 and 2 were reperfused for ten minutes with unmodified blood at 30°C and 50 mm Hg root pressure, followed by perfusion for two hours at 37°C and 100 mm Hg. Group 3 received ten minutes of modified warm blood cardioplegia containing glutamate under the same pressure and temperature conditions as in groups 1 and 2, followed by two hours of normothermic perfusion at 100 mm Hg. The composition of the modified blood cardioplegia is as follows:

K = 22 mEq/L
Na = 80–100 mEq/L
Cl = 80–100 mEq/L
Ca = 0.3 mEq/L
Hematocrit = 10–20%
L-Glutamate = 26 mmol/L
Osmolality = 360 mosm/L
pH (30°C) = 7.8

Myocardial biopsy specimens for determination of heart water content were taken immediately after excision and preservation, as well as at the termination of two hours of

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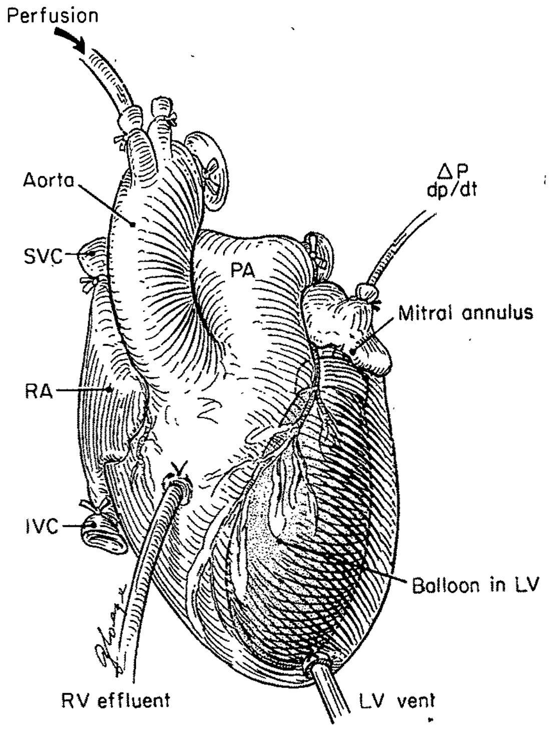

*Fig 1. Isolated blood-perfused canine heart. (*ΔP = *left ventricular developed pressure;* dp/dt = *rate of rise of left ventricular pressure;* IVC = *inferior vena cava;* LV = *left ventricle;* PA = *pulmonary artery;* RA = *right atrium;* RV = *right ventricle;* SVC = *superior vena cava.)*

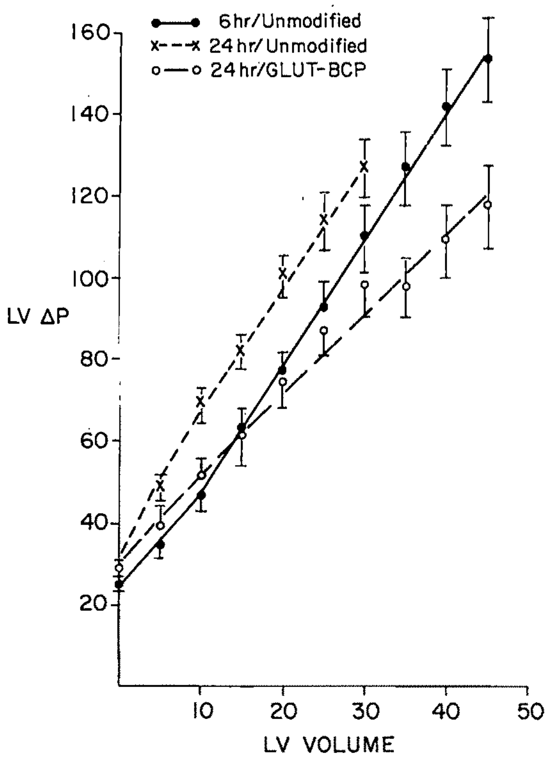

Fig 2. Left ventricular (LV) *function curves after two hours of reperfusion: developed pressure* (LV ΔP) *in groups 1* (6 hr/Unmodified), 2 (24 hr/Unmodified), *and 3* (24 hr/GLUT-BCP) *versus volume.*

Table 1. Hemodynamic Measurements[a]

Group	LVDP[b] (mm Hg)	dP/dt_{max} (mm Hg/s)	Diastolic Compliance (mm Hg/mL)
1	110 ± 15	1,456 ± 171	0.504
2	127 ± 14	1,905 ± 395	1.395
3	98 ± 13	1,450 ± 291	0.776[c]

[a] Where applicable, data are shown as the mean ± the standard error of the mean. [b] These measurements are at a balloon volume of 30 mL. [c] Significance: $p < 0.02$ versus group 2.

LVDP = left ventricular developed pressure; dP/dt_{max} = maximum rate of rise of left ventricular pressure.

reperfusion. Myocardial performance was assessed using an intraventricular balloon to determine compliance and ventricular function after 30 and 60 minutes of reperfusion (Fig 1).

Results were expressed as the mean ± the standard error of the mean. Analysis of variance was used to test the differences in means among all three groups. Student's *t* test was used between groups when analysis of variance showed significant differences. A *p* value of less than 0.05 was considered significant.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

Group 1 was used as the control because previous studies [10, 11] have indicated excellent recovery after short-term hypothermic preservation. Left ventricular function was noted to be similar for all groups (Fig 2), with left ventricular developed pressure of 110 ± 15 mm Hg in group 1, 127 ± 14 mm Hg in group 2, and 98 ± 13 mm Hg in group 3 at a balloon volume of 30 mL (Table 1). In addition, when tested individually, the means for a given volume in groups 2 and 3 were not found to be significantly different.

Left ventricular function as reflected by maximum rate of rise of left ventricular pressure was also similar in all groups (1,456 ± 171 mm Hg/s in group 1, 1,905 ± 395 mm Hg/s in group 2, and 1,450 ± 291 mm Hg/s in group 3). Diastolic compliance curves were similar in groups 1 and 3, and were significantly improved compared with group 2 (0.504 mm Hg/mL and 0.776 mm Hg/mL versus 1.395 mm Hg/mL; $p < 0.02$) (Fig 3).

After 24 hours of preservation, before reperfusion, there was no significant difference in myocardial water content of groups 2 and 3 hearts (77.5 ± 0.3 versus 78.1 ± 0.5) compared with group 1 hearts (76.2 ± 0.5) (Table 2). After two hours of reperfusion, gain in water content was noted in each group, with similar postreperfusion edema in all 3 groups.

Comment

Successful long-term preservation of the myocardium depends on methods that avoid ischemic damage during preservation and prevent or reverse reperfusion injury. Several studies have examined prolonged cold storage of hearts without perfusion with subsequent evaluation of function. Griepp and associates [16] stored hearts in a nonperfused intracellular (Collins') solution at 4°C for 12 hours, with subsequent orthotopic transplantation. The average survival was 21 hours, with poor myocardial function as the primary cause of death.

Reitz and associates [17] examined the function of hearts stored at 4°C in three different solutions, an extracellular solution (Krebs) and two intracellular solutions (Collins' and Sacks). The hearts were stored for 18 to 26 hours, followed by orthotopic transplantation. None of the hearts stored in Krebs solution functioned; however, 22% of the hearts stored in Collins' or Sacks solution functioned until homograft rejection.

Thomas and co-workers [18] demonstrated a long-term survival of 93% in heterotopically transplanted hearts after 24-hour nonperfused storage at 4°C in Sacks solution modified with mannitol and glucose. Myocardial cellular architecture was well maintained by light and electron microscopy. However, it should be noted that these hearts were heterotopically transplanted.

Toledo-Pereyra and colleagues [3] compared 24-hour nonperfused storage of canine hearts at 7°C in three solutions—Ringer's lactate, Sacks, and a modified silica gel fraction (a hyperosmolar, hyperkalemic, hyperglycemic solution)—followed by heterotopic transplantation. Hearts stored in Ringer's lactate had almost no function and were markedly damaged on microscopic examination, but those stored in Sacks and silica gel fraction solutions demonstrated prolonged viability with mild to moderate cellular disruption. Again, these hearts were evaluated only by heterotopic transplantation.

Watson [19] found a 33% prolonged survival in nonperfused, orthotopically transplanted hearts stored for 24 hours at 3°C in a hypertonic intracellular solution. English and co-workers [20] stored pig hearts for 16 hours in a cold (4°C) cardioplegic solution with subsequent orthotopic transplantation; 50% of the animals survived six hours to 83 days. Swanson and associates [21], using an extracorporeal working heart preparation, evaluated hearts preserved for 24 hours at 4°C in a nonperfused modified Collins' solution and found an average of 75% recovery of baseline function.

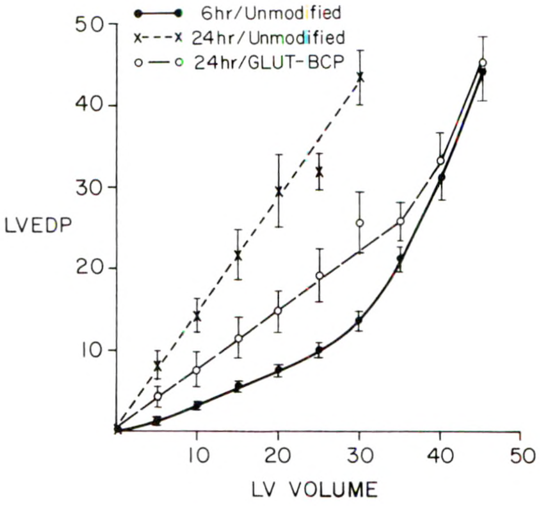

Fig 3. Left ventricular (LV) compliance curves after two hours of reperfusion: end-diastolic pressure (LVEDP) in groups 1 (6 hr/Unmodified), 2 (24 hr/Unmodified), and 3 (24 hr/GLUT-BCP) versus volume.

Table 2. Myocardial Water Content[a]

Group	Excision	Preservation	Reperfusion
1	75.0 ± 1.0	76.2 ± 0.5	78.4 ± 0.6
2	76.2 ± 0.5	77.5 ± 0.3	80.1 ± 0.4
3	74.7 ± 0.7	78.1 ± 0.5	79.6 ± 0.6

[a] Data are shown as percentages.

In light of the less than optimal results obtained with various preservative solutions in these and other studies, modifications in reperfusion of the stored heart were examined in an effort to further improve cardiac function. Swanson and associates [15] found that a modified blood reperfusate with 36 mEq/L of potassium chloride, 50 mEq/L of glucose, an osmolarity of 410 mosm, and pH of 7.7 resulted in a 93% recovery of left ventricular function in an isolated working heart model. This was presumably achieved by a reduction in reperfusion injury or enhanced restoration of cellular function by (1) preventing a large sodium influx by partial depolarization with potassium chloride in the perfusate, thus minimizing cellular edema, (2) preventing intracellular calcium accumulation by decreasing free calcium in the perfusate, and (3) increasing subendocardial perfusion by preventing fibrillation. Deleting potassium chloride from the modified perfusate resulted in sodium accumulation, edema, and poor ventricular function. In this study, reperfusion was maintained for 45 minutes, which may present a drawback in clinical applicability.

Buckberg and co-workers [12–14] demonstrated that after short-term ischemic injury, administration of warm blood cardioplegia improved recovery and allowed increased oxygen utilization for reparative processes rather than electromechanical work. In addition, reperfusion with substrate-enriched cardioplegia enhanced oxygen uptake and repletion of adenosine triphosphate after ischemic injury by providing necessary cellular substrates for aerobic metabolism.

In the present study, reperfusion with warm glutamate-enriched blood cardioplegia after prolonged hypothermic storage improved diastolic compliance of the left ventricle compared with reperfusion with an unmodified reperfusate, while preserving systolic function. This suggested that reperfusion injury was diminished and edema formation limited, findings in accordance with those of the studies already discussed. In addition, the degree of ischemic contracture contributing to wall stiffness may have been lessened by the modified reperfusate in group 3. However, the modified reperfusate was unable to reduce edema formation beyond that seen with unmodified blood. The results of this study indicate that the modification of the reperfusate ameliorates reperfusion damage and thus, reperfusion remains a valuable adjunct to long-term preservation. However, further attention must be focused on limiting ischemic injury during prolonged storage and reperfusion.

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Right Ventricular Free Wall Ischemia: Correlation of Ischemic Duration With Extent of Infarction in Dogs

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The time dependence of myocardial necrosis has not been established for the right ventricle. In 16 dogs, we studied the temporal extension of ischemia-induced right ventricular free wall infarction for one hour (n = 8) and two hours (n = 8) followed by two hours of reperfusion, and quantitated segmental shortening, area at risk from ischemia, and area of necrosis. Stroke volume decreased 7.3 ± 0.5 mL/beat (± standard error of the mean) in one hour ($p < 0.05$) and 7.4 ± 1.3 mL/beat in two hours ($p < 0.05$). Segmental shortening was replaced by paradoxical motion in both groups during ischemia, and remained depressed throughout reperfusion. Right ventricular end-diastolic pressure increased with ischemia and then returned to normal during reperfusion. The extent of infarction appeared proportionate to the duration of ischemia, 13.2% ± 4.1% at one hour and 66.9% ± 4.5% at two hours ($p < 0.01$). We conclude that the wave front of necrosis in the right ventricle progresses with duration of ischemia and that clinical techniques capable of limiting the duration of ischemia might salvage substantial amounts of right ventricular myocardium.

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The duration of ischemia represents a major factor determining the extent of myocardial necrosis in experimental studies of the left ventricle [1, 2], but a similar correlation for the right ventricle has not been established. The right ventricle is reported to be more resistant to ischemic injury than the left ventricle because of its lower metabolic demands from its lower intracavitary pressure and wall tension [3, 4]. In addition, the right ventricular free wall receives 25% to 33% of its total blood flow by way of collateral perfusion from branches of the left anterior descending and circumflex coronary arteries [5, 6]. We [7] have previously shown that this collateral perfusion can provide sufficient nutrient flow to limit the extent of infarction. Consequently, the assumption made for the left ventricle that myocardial necrosis progresses with time may not necessarily be correct for the right ventricle.

Whether right ventricular necrosis is time dependent has clinical relevance, as recent techniques, such as surgical revascularization, thrombolysis, or coronary angioplasty, can reestablish flow to ischemic areas of the myocardium. The application of these techniques in patients with acute right ventricular ischemia is based on the assumption that limiting the duration of ischemia will subsequently lessen the amount of necrotic damage. Accordingly, in an anesthetized canine model, we tested the hypothesis that the extent of right ventricular necrosis is indeed proportional to the duration of ischemia.

Material and Methods

Experimental Preparation

Eighteen microfilaria-free mongrel dogs (mean weight, 19.9 ± 0.9 kg; range, 12.5 to 25.5 kg) were handled in the laboratory in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). The institutional animal care and use committee approved this study.

General anesthesia was induced with sodium pentobarbital, 30 mg/kg intravenously, and each animal was ventilated with a tidal volume of 18 mL/kg through a cuffed endotracheal tube attached to a Harvard volume-cycled ventilator (model 607; Harvard Apparatus, Dover, MA). The respiratory rate was adjusted to achieve normocarbia, and the inspired oxygen concentration was adjusted to maintain an arterial oxygen tension greater than 100 mm Hg. Supplemental pentobarbital was administered by a constant infusion of 2 to 4 mg/kg/h. Succinylcholine chloride (0.5 mg/kg intravenously) was administered for muscle paralysis to ablate spontaneous respiratory effort.

Catheters (inner diameter, 1.67 mm) were inserted into the femoral artery and vein, and a thermodilution catheter was inserted through the external jugular vein into the pulmonary artery. With the animal in the supine position, the thorax was opened through a median sternotomy incision. Through the right upper lobe pulmonary vein, a catheter was inserted into the left atrium and its position confirmed by transduced waveform. Millar MPC-500 transducer-tipped catheters (Millar Instruments, Inc, Houston, TX) were inserted into the right ventricle

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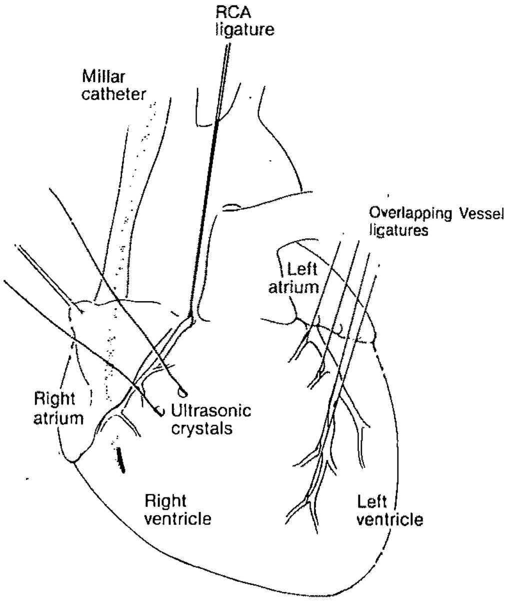

Fig 1. Model of right ventricular ischemia. Loose suture ligatures were placed around the right coronary artery (RCA) *and epicardial overlapping vessels perfusing the right ventricular free wall. (See text for details.)*

through the external jugular vein and into the ascending aorta through the right internal mammary artery.

The pericardium was opened from the pericardial reflection at the base of the aorta to the right ventricular apex and tented. The right coronary artery (RCA) was isolated near its origin proximal to the pulmonary conus branch and loosely encircled with a rubber snare (Fig 1). Loose suture ligatures were placed around visible overlapping arterial branches from the left anterior descending and circumflex coronary arteries that extended to the right ventricular free wall. Near the center of the right ventricular free wall, two ultrasonic dimension transducers were implanted parallel to the direction of fiber shortening (see Fig 1). The ultrasonic signals were received and analyzed instantaneously to measure the distances between crystals (model 301 sonomicrometer; Triton Technology, Inc, San Diego, CA). Proper crystal alignment was determined by observing the input and output signals from the sonomicrometer on a dual-trace oscilloscope (model 2213A; Tectronix, Inc, Beaverton, OR).

The pericardium was reapproximated edge to edge with care taken to minimize overlap and prevent constriction. The cables from the ultrasonic crystals and the ends of the coronary snares were brought out through an opening near the aorta. During instrumentation, the animal received 20 mL/kg of lactated Ringer's solution followed by a continuous infusion of 7 to 10 mL/kg/h. Arterial blood gases were measured repeatedly (model 1302 blood gas analyzer; Instrumentation Laboratories, Lexington, MA) to ensure normocarbia and absence of hypoxemia. Arterial pH was maintained at 7.40 ± 0.05 by administering sodium bicarbonate as needed. Body temperature was maintained at 37° ± 1°C using a heated humidifier and external heating blanket.

All pressures were recorded by Gould fluid-filled transducers and micromanometer-tipped catheters connected to a Gould ES 1000-B electrostatic recorder. Transducers were zeroed against atmospheric pressure at the anterior axillary level and calibrated with a mercury manometer attached to all transducers by a common manifold system. The hemodynamic variables recorded at end-expiration included mean arterial pressure, right ventricular systolic and diastolic pressures, left atrial pressure, segmental shortening, heart rate, blood temperature, and lead II of the electrocardiogram. Right ventricular end-diastolic and end-systolic dimensions were recorded just before peak positive and peak negative rate of rise of left ventricular pressure, respectively [8]. Segmental shortening (percent) was calculated as follows: [(end-diastolic length − end-systolic length)/end-diastolic length] × 100. Mean cardiac output was determined by thermodilution from three injections of 5 mL of iced saline solution.

Regional myocardial blood flow at each time period was measured using radioactive microspheres 15 ± 3 μm in diameter (3M Company, St. Paul, MN, and New England Nuclear Corporation, Billerica, MA) labeled with gadolinium 153, strontium 85, scandium 46, chromium 51, or tin 113. The microspheres were thoroughly sonicated, diluted in 3 mL of saline solution, and centrifuged. Over 30 seconds, approximately 2 to 3 million microspheres were injected through the left atrial catheter followed by a 5-mL flush injection. With a constant-withdrawal pump started 30 seconds before microsphere injection and continued for three minutes after injection, the reference sample was aspirated from the femoral artery catheter at a rate of 6.5 mL/min. One-minute samples were collected in separate tared vials to ensure that the fourth sample was free from radioactivity.

Experimental Protocol

All dogs received heparin sodium, 300 U/kg intravenously, followed by 100 U/kg every hour thereafter. In addition, before the baseline measurements were made, each dog received lidocaine hydrochloride, 1.3 mg/kg intravenously, followed by an infusion of 0.3 mg/min throughout the experiment. Lidocaine, in 10-mg doses, was administered thereafter as necessary for the suppression of ventricular dysrhythmias.

The 18 dogs were randomly divided into two groups, both having right ventricular ischemia established by ligation of the RCA and overlapping vessels extending from the left ventricle. A previous study from this laboratory [7] confirmed that this technique of experimental right ventricular ischemia increases the predictability and extent of right ventricular free wall necrosis. One group of dogs (n = 9) had one hour of occlusion and one group (n = 9), two hours of occlusion. In both groups, occlusion was followed by two hours of reperfusion. Hemodynamic measurements, including the microspheres, were obtained at baseline, during the last 15 minutes of the ischemic period, and at 15, 60, and 120 minutes into the reperfusion period.

At the conclusion of each experiment, the ligatures were retightened around the RCA and the overlapping vessels from the left ventricle, and 2% gentian violet

Table 1. Hemodynamic Variables During Right Ventricular Ischemia and Reperfusion

				Reperfusion (min)		
Variable	Group	Baseline	Ischemia	15	60	120
Mean arterial pressure (mm Hg)	1	99.7 ± 3.1	87.0 ± 5.7[a]	94.2 ± 3.5	93.3 ± 5.5	87.3 ± 5.0
	2	95.9 ± 4.6	87.6 ± 3.5	86.0 ± 5.0	81.8 ± 4.4[a]	81.8 ± 5.0
Stroke volume (mL/beat)	1	22.0 ± 2.4	14.7 ± 1.9[a]	16.1 ± 1.3[a]	17.2 ± 1.7[a]	15.8 ± 2.2[a]
	2	24.0 ± 2.8	16.6 ± 1.5[a]	18.8 ± 2.2	16.9 ± 0.7[a]	16.2 ± 0.8[a]
RV end-diastolic pressure (mm Hg)	1	5.6 ± 0.6	8.9 ± 0.9[a]	7.1 ± 0.9[a]	5.7 ± 0.7[b]	6.8 ± 0.9
	2	5.5 ± 0.4	7.4 ± 0.6[a]	7.0 ± 0.6[a]	6.6 ± 0.8	5.6 ± 0.4[b]
Left atrial pressure (mm Hg)	1	6.8 ± 0.8	7.9 ± 0.4	7.6 ± 0.7	6.9 ± 0.6	7.8 ± 0.8
	2	7.9 ± 0.6	8.3 ± 0.5	8.3 ± 0.6	8.6 ± 0.8	7.5 ± 0.7
Segmental shortening (%)	1	7.4 ± 0.9	−2.0 ± 0.8[a]	2.8 ± 1.1[a,b]	2.8 ± 1.3[a,b]	1.5 ± 1.2[a,b]
	2	12.1 ± 2.1	−1.2 ± 0.9[a]	0.7 ± 0.9[a]	0.3 ± 0.8[a]	0.5 ± 0.8[a]

[a] Significance: $p < 0.05$ compared with baseline [b] Significance: $p < 0.05$ compared with ischemia.

RV = right ventricular.

solution (0.15 mL/kg) was injected through the left atrial catheter and allowed to circulate for 15 seconds to outline the area at risk. Each animal then received a lethal injection of potassium chloride.

The heart was excised and blotted dry. The right ventricular free wall was divided at its junction with the interventricular septum and sectioned into subendocardial and subepicardial halves. Each section was incubated for 20 minutes in a solution of triphenyltetrazolium chloride (TTC) warmed to 37°C. The portion of the right ventricular free wall that contained gentian violet was considered normally perfused, whereas the section that was unstained represented the area at risk from myocardial ischemia. Within the area at risk from ischemia, the part that was pale was considered necrotic [9, 10]. (The sensitivity of TTC to identify myocardial necrosis has been verified by histological examination under light [11, 12] and electron [13] microscopy.) The TTC precipitates in the presence of intact dehydrogenase enzyme systems, so that normal myocardium is stained brick red, and necrotic areas, by failing to stain, appear pale. (The TTC staining technique has been shown to be an accurate method of assessing infarct size [12].) The pale areas of necrosis were carefully excised with the angle of the scissors being guided by the stained margins on both sides of the specimen, as described previously [7].

Tissue samples from each region (normally perfused, area at risk without infarction, and infarcted area) were placed into tared vials, weighed, and analyzed separately for regional blood flow. Percent necrosis was determined gravimetrically as the weight of necrotic tissue relative to the weight of the area at risk. This method of infarct sizing has been used previously in the right ventricle [7], and is similar to the planimetric-gravimetric technique used by others [14, 15]. To further assure its validity, we compared gravimetric analysis with conventional planimetry in 3 dogs (not among the 18 animals studied) and found close correlation between the two techniques over a wide range of infarct sizes (ie, 9.4% versus 8.4%; 52.1% versus 49.9%; and 28.1% versus 23.9%, respectively).

Statistical Analysis

Data (expressed as mean ± standard error of the mean) were examined by analysis of variance to assess differences between groups at baseline. Differences between groups during ischemia and reperfusion were assessed using analysis of covariance adjusted for baseline values. Differences within a group between measurement periods were analyzed by linear-models analysis of variance for repeated measures. A p value less than or equal to 0.05 was considered significant.

Results

Among the 18 dogs entered into the study, the experiment was successfully completed in 16 (89%). One dog in the two-hour group was excluded for technical reasons; 1 dog in the one-hour group had a congenital malformation of the pericardium that prevented closure. Ventricular dysrhythmias were common during ischemia and especially during the early phase of reperfusion. These dysrhythmias usually responded to lidocaine. Four dogs (3 in the one-hour group and 1 in the two-hour group) had ventricular fibrillation during reperfusion. In all 4 dogs, the fibrillation was converted with direct-current countershock within one minute.

Table 1 shows hemodynamic data during ischemia and reperfusion. Acute occlusion of the RCA and overlapping vessels reduced mean arterial pressure similarly in both groups. Right ventricular end-diastolic pressure increased significantly during ischemia but became normal during reperfusion. In contrast, the significant decrease in stroke volume with ischemia persisted throughout reperfusion. Heart rate did not change with ischemia or reperfusion in either group. The central venous waveform pattern gave no evidence of tricuspid regurgitation in any dog.

The ultrasonic dimension transducers were located in areas at risk from ischemia in all animals, as demonstrated by the absence of gentian violet staining in the tissue surrounding the transducers. During ischemia, regional segmental shortening demonstrated paradoxical bulging (see Table 1). Similar to stroke volume measurements, segmental shortening remained depressed in both groups during reperfusion.

In the uninfarcted right ventricular area at risk, blood flow to the subendocardial and subepicardial layers decreased significantly in both groups during ischemia (Fig 2). During the first 15 minutes of reperfusion, there was a trend toward hyperemia in both groups, with restoration to preocclusion levels by two hours of reperfusion. In the area that ultimately sustained infarction, perfusion to subendocardial and subepicardial layers decreased similarly in both groups ($p < 0.05$) during ischemia (Fig 3). During 15 minutes of reperfusion, flow significantly exceeded baseline values in both subendocardial and subepicardial layers in the one-hour group. In contrast, this flow response was significantly attenuated in the two-hour group. However, by two hours of reperfusion, regional blood flow was comparable with control values in both groups.

The size of the right ventricular free wall was similar (28.8 ± 2.5 g in the one-hour group and 31.7 ± 2.8 g in the two-hour group). The area at risk from ischemia, expressed as a percentage of the free wall, was significantly greater in the two-hour group than in the one-hour group (76.2% ± 1.9% versus 70.0% ± 2.5%; $p < 0.05$). The extent of infarction appeared proportionate to the duration of ischemia, the two-hour group having a significantly greater amount of necrosis (66.9% ± 4.5% versus 13.2% ± 4.1%; $p < 0.01$). The range of the area of necrosis relative to the area at risk was 0% to 34.7% for the one-hour group and 50.5% to 85.1% for the two-hour group. In both groups, the distribution of necrosis between the subendocardium and the subepicardium was similar, 1.1 ± 0.4 and 1.5 ± 0.6 g, respectively, for the one-hour group and 7.7 ± 0.6 and 8.5 ± 1.3 g, respectively, for the two-hour group.

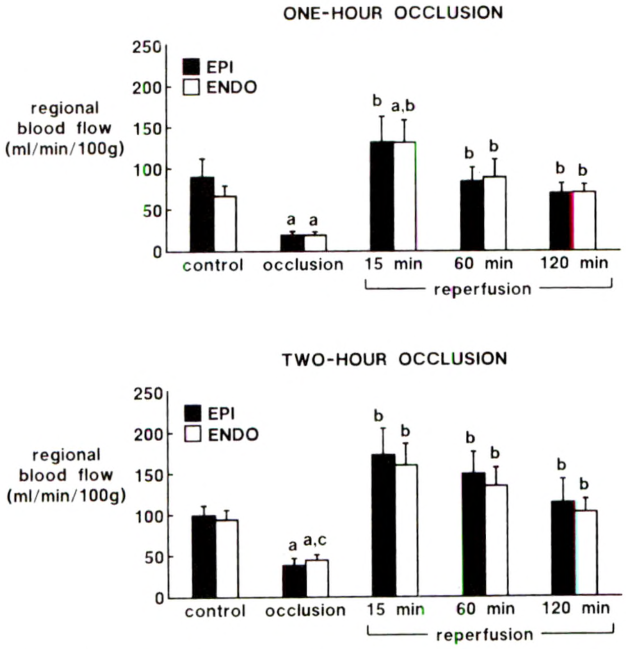

Fig 2. Regional myocardial blood flow in the uninfarcted area at risk for group 1 (one-hour occlusion) and group 2 (two-hour occlusion) animals. (a = $p < 0.05$ *compared with control;* b = $p < 0.05$ *compared with ischemia;* c = $p < 0.05$ *compared with corresponding one-hour value;* ENDO = *subendocardium;* EPI = *subepicardium.)*

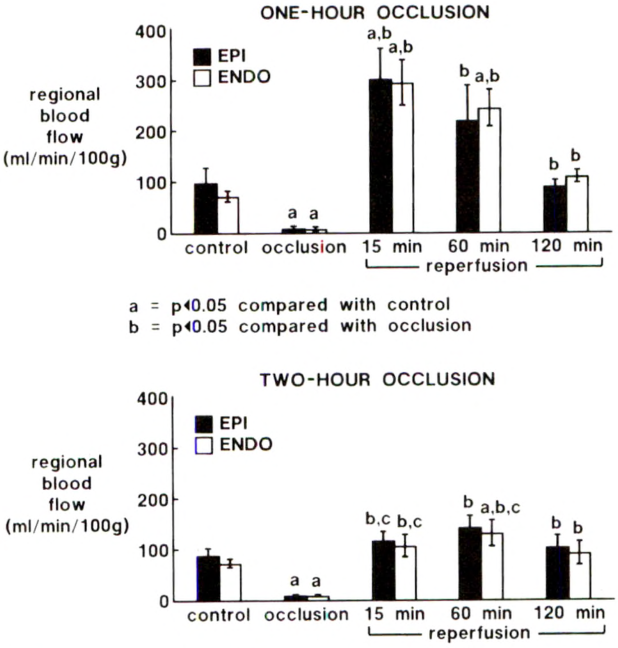

Fig 3. Regional myocardial blood flow in the infarcted area for group 1 (one-hour occlusion) and group 2 (two-hour occlusion). Note that early postischemic reactive hyperemia, which was evident after one hour of right coronary artery occlusion, was absent after two hours of right coronary artery occlusion. (a = $p < 0.05$ *compared with control;* b = $p < 0.05$ *compared with occlusion;* c = $p < 0.05$ *compared with corresponding one-hour value;* ENDO = *subendocardium;* EPI = *subepicardium.)*

Comment

Factors known to aggravate ischemia in the left ventricle cannot be assumed to apply equally to the right ventricle unless the determinants of oxygen supply and demand can be shown to be similar for both ventricles. It is known that alterations in the regional distribution of blood flow during ischemia differ between the two ventricles. Ohzono and colleagues [16] and Hess and Bache [17] found that right ventricular free wall blood flow in dogs decreased to the same extent in subepicardial and subendocardial layers after occlusion of the RCA. In contrast, in the left ventricle, occlusion of the circumflex artery decreased flow to the subendocardium to a greater extent than flow to the subepicardium.

In terms of oxygen demand, Kusachi and associates [4], studying a canine model, showed that the right ventricle, as a result of its lower intraventricular pressure and lower wall stress, required less blood flow and extracted less oxygen than the metabolically more active left ventricle. The thinner wall and smaller muscle mass of the right ventricle may render it less susceptible to ischemia than the left ventricle.

These studies and that of Urabe and colleagues [3] suggest that the right ventricle can tolerate a lower coronary perfusion pressure than the left ventricle before developing ischemia. An additional factor is that 25% to 37% of the right ventricular free wall margins are supplied by overlapping vessels originating from the left anterior descending and circumflex coronary arteries [5, 6]. Thus, compared with the left ventricle, the right ventricle should be relatively resistant to ischemia, and factors affecting the severity of ischemia may be different for the two ventricles.

Results of other canine studies, however, suggest that the ventricles are equally sensitive to myocardial ischemia. Using adenine nucleotide metabolism as an indicator of energy production and utilization, Morris and associates [18] found a similar depletion of nucleotides in both ventricles subjected to ischemia. Relative to the left ventricle, the right ventricle appeared as sensitive to ischemia and required as long a recovery period. Ohzono and colleagues [16] found that both the right and the left ventricle had similar percentages of necrosis relative to the area at risk after 24-hour occlusion of the RCA or obtuse marginal artery. Thus, although oxygen demand may be less in the right ventricle, severe ischemia of that ventricle, such as was produced in our study, does cause major infarction.

Our results may have been influenced by our concomitant ligation of overlapping vessels in addition to the RCA, which probably increased the amount of myocardium subjected to flow deprivation. However, because the same model was used for both one-hour and two-hour ischemia, we conclude that the extent of necrosis in the right ventricle increases with the duration of ischemia, similar to the left ventricle [2].

One difference between the response of the ventricles to ischemia can be seen in the progression of the necrosis. With left coronary artery occlusion in dogs, a wave-front pattern of necrosis develops, beginning in the subendocardium and extending toward the subepicardium as the occlusion continues [19, 20]. The greater vulnerability of the subendocardium to myocyte necrosis [2, 19] may be due either to greater deprivation of blood flow from higher intramural compressive forces in the subendocardium or to greater oxygen consumption in the subendocardium than in the subepicardium [21].

Data from the present study and a previous study [7] confirm the equal deprivation of perfusion to the right ventricular subendocardium and subepicardium, as reported by Ohzono and co-workers [16] and Hess and Bache [17]. With one hour and two hours of ischemia, we found similar areas of necrosis in both subendocardial and subepicardial layers. Whether a lateral progression of necrosis exists in the severely ischemic right ventricle, in contrast to a transmural progression in the left ventricle, requires further study.

Our findings contrast with those in other studies, in which right ventricular free wall injury was caused by electrocautery, which indicated the right ventricle was unimportant to overall circulatory homeostasis [22–24]. However, the electrocautery injury may have been primarily subepicardial in nature [25], as there is considerable experimental evidence that the right ventricular free wall plays a prominent role in right ventricular ejection [26–28]. Furthermore, the pericardium was removed or was left open in those studies, which could have allowed a substantial increase in right ventricular volume without a corresponding increase in pressure [28]. In our study, the pericardium was closed, which may have potentiated the hemodynamic consequences of right ventricular ischemia.

Our study also contrasts with other studies of right ventricular ischemia in that the heart was not reperfused in those studies [16, 29, 30]. Staining with TTC requires the washout of hydride carriers from irreversibly damaged myocardium. With ischemia alone, collateral blood flow in the center of the evolving infarct is required to wash out cofactors necessary for the TTC reaction [12]. The process is considerably accelerated by reperfusion [9], which is why two hours of reperfusion were used in this study. Reperfusion also accelerates the progression of postischemic dysfunction [31].

In the area that developed necrosis, reperfusion to both the subendocardium and the subepicardium showed a significant reactive hyperemia in the one-hour group after 15 minutes of reperfusion that was absent in the two-hour group. Whether this finding represents a "no-reflow phenomenon" and contributes to the greater extent of necrosis after two hours of ischemia warrants further study. The no-reflow phenomenon in the left ventricle has been attributed to swelling of endothelial cells, intraluminal bleb formation, capillary plugging by neutrophils, and parenchymal swelling with capillary compression [32–34]. Kloner and associates [33] noted a nonuniform distribution of reperfusion flow—primarily to the subendocardium—after 90 minutes of left ventricular ischemia. In contrast, after 60 minutes of right ventricular ischemia, we found equal subendocardial and subepicardial flow during reperfusion in the right ventricular free wall.

In patients, right ventricular infarction frequently coexists with left ventricular inferior wall infarction, thereby resulting in biventricular and possibly septal involvement. In addition, our model of acute coronary occlusion does not allow the development of collateral vessels as would occur during gradual blockage of the main coronary arteries. Therefore, the hemodynamic findings in the present study should not be extrapolated directly to patients with myocardial ischemia. Rather, the value of our findings is that they provide insight into the pathophysiological basis of experimental right ventricular ischemia by demonstrating a progression of necrosis as the duration of ischemic injury lengthens. Right ventricular necrosis is influenced both by the degree and by the duration of flow deprivation. Consequently, on the basis of our findings, methods that limit the duration of ischemia in the right ventricle, such as surgical revascularization, thrombolysis, or coronary angioplasty, could limit expansion of infarction, although derangements in hemodynamic variables might persist.

We conclude that the wave front of necrosis in the canine right ventricle increases with the duration of ischemia and that there is equal involvement of the subendocardial and subepicardial layers. Right ventricular ischemia causes regional wall dysfunction and persistent hemodynamic derangements that appear independent of the amount of free wall necrosis.

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Hospital Costs and Resource Characteristics for Cardiothoracic Surgical Hospital Deaths

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No major changes in the federal Medicare diagnostic-related group (DRG) prospective hospital payment system have been implemented by the United States Congress. We analyzed hospital resource consumption for 1,567 cardiothoracic surgical patients by outcome (ie, survivors versus nonsurvivors). The 76 patients who died had a much greater intensity of hospital resource utilization and represented a substantial financial risk under DRG pricing schemes compared with the 1,491 survivors. Only patients who died within 1 week of admission to the hospital generated a financial surplus under DRGs. A long hospital stay for nonsurvivors produced a substantial deficit (patients with a stay greater than 60 days generated a $154,433 loss per patient). The cardiothoracic patients admitted on an emergency basis who died tended to have a shorter length of stay and represented a lower financial risk under DRGs compared with patients admitted on a nonemergency basis who died. Among nonsurvivors, patients referred for cardiothoracic surgical procedures from other clinical services had lower resource utilization and financial risk under DRGs compared with nonreferrals. These data suggest significant inequities in the current DRG prospective payment system vis-à-vis cardiothoracic surgical patients who die. Variables predictive of greater hospital resource utilization by outcome included a longer hospital stay, nonemergency admission, and admission directly to the cardiothoracic surgical service. Methods to improve the equity of DRG payment vis-à-vis cardiothoracic surgical nonsurvivors should be implemented in the future.

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A number of important health policy questions face the United States regarding the federal Medicare diagnostic-related group (DRG) prospective hospital payment system [1]. Despite many studies and criticisms, there have been no major changes in the DRG system since its inception in 1983 [2]. The DRG system has been criticized for inaccurate resource prediction [3]. Supporters of the current DRG scheme claim that any system that groups 10 million annual Medicare hospitalizations into fewer than 500 mutually exclusive categories is based on "average prediction" at best. As of the most recent federal regulations, there are 477 DRGs [2].

One key component for DRG fairness is providing adequate hospital reimbursement at the institutional level (ie, hospital specific). Hospitals thought to treat more severely ill patients or patients requiring more expensive treatment, such as teaching and public hospitals, receive an additional DRG subsidy [4, 5]. Some health policy experts believe, however, that the DRG system must be reasonably accurate at the patient level, especially for physicians to use it. Nonetheless, recent federal regulations have made no major changes to improve DRG equity along the lines of severity of illness, outcome, or outliers (ie, patients requiring very expensive treatment).

None of the 250 surgical DRGs are stratified by outcome (survivors versus nonsurvivors); a few medical DRGs are stratified by outcome. Those so stratified are cardiology DRGs: No. 121, circulatory disorders with acute myocardial infarction with complications, discharged alive; No. 122, circulatory disorders with acute myocardial infarction without complications, discharged alive; and No. 123, circulatory disorders with acute myocardial infarction, died. There is evidence to suggest that patients who undergo a surgical procedure and die in the hospital generate financial risk under DRG pricing schemes [6].

The purpose of this study was to analyze hospital resource consumption for a large group of cardiothoracic surgical patients who died. The following factors were examined: route of admission (emergency versus nonemergency), age, length of hospital stay (LOS), and change in clinical service.

Material and Methods

The Long Island Jewish Medical Center is an 805-bed urban teaching hospital in suburban New York City. We analyzed all adult patients in our major operative cardiothoracic surgical DRGs from January 1, 1985, to December 31, 1987, in terms of a number of resource characteristics for survivors (those discharged alive from the hospital) and nonsurvivors (those who died in the hospital). The DRGs included are shown in Table 1.

The variables measured per patient were the following: age (years), LOS (days), mean total hospital cost, mean total hospital cost per day, profit or loss under the Medicare DRG reimbursement scheme (ie, using Medi-

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Table 1. Diagnostic-Related Groups Analyzed

DRG	Description	DRG Weight Index
075	Major chest procedures	2.5773
083	Major chest trauma, age >69 years, and/or complicating condition	0.9707
084	Major chest trauma, age <70 years, without complicating condition	0.7658
104	Cardiac valve procedure with pump and cardiac catheterization	6.7815
105	Cardiac valve procedure with pump and without cardiac catheterization	5.1764
106	Coronary bypass with cardiac catherization	5.2077
107	Coronary bypass without cardiac catheterization	3.9476
108	Cardiothoracic procedure except valve and bypass with pump	4.3301
109	Cardiothoracic procedure without pump	3.6579

DRG = diagnostic-related group.

Table 2. Resource Characteristics for Survivors and Nonsurvivors (Cardiothoracic Surgery)[a]

Variable	Survivors (n = 1,491)	Nonsurvivors (n = 76)
Age (yr)	52.3	49.1
DRG weight index	4.4242	4.2544
Length of hospital stay (days)	15.1[b]	29.5
No. of diagnoses[c]	3.38[b]	6.21
No. of procedures[c]	4.82[b]	6.61
Total ICD-9-CM codes	8.20[b]	12.82
Total hospital cost	$18,221[b]	$47,235
Hospital cost per day	$1,272[b]	$2,475
Profit/loss[d]	$6,119[b]	($21,412)
Emergency room admissions (%)	14.0[e]	25.0
SICU admissions (%)	100	100
Blood transfused (%)	68.9[e]	86.8

[a] Data are shown as the mean per patient. [b] Significance: $p < 0.0001$ versus nonsurvivors. [c] This is the number of ICD-9-CM codes per patient. [d] This is the mean profit or loss per patient under DRG payment; data in parentheses equal loss. [e] Significance: $p < 0.009$ versus nonsurvivors.

DRG = diagnostic-related group; SICU = surgical intensive care unit.

care DRG payment rates) and standard New York State DRG methodology outliers, route of admission (emergency versus nonemergency), number of ICD-9-CM diagnosis codes, number of ICD-9-CM procedure codes, total number of ICD-9-CM codes (as a proxy for severity of illness), and certain clinical variables, such as surgical intensive care unit admission and requirement for blood or plasma products (except during cardiopulmonary bypass). A previous study by our group [7] demonstrated that the number of ICD-9-CM diagnosis codes per surgical patient could function as a proxy for increasing hospital cost and increasing mortality. However, this severity proxy has several shortcomings. In particular, it is a retrospective severity instrument and may be biased toward diagnostic or treatment failures. It was, however, the only accessible and reproducible method to assess severity available in our hospital data base.

Patients who died were analyzed in a number of ways: LOS—one to seven days, eight to 14 days, 15 to 21 days, 22 to 30 days, 30 to 60 days, and more than 60 days; route of admission (emergency versus nonemergency); change in clinical service (referred to the cardiothoracic surgical service from a noncardiothoracic surgical service); age (years)—18 through 24, 25 through 34, 35 through 44, 45 through 54, 55 through 64, 65 through 69, 70 through 74, 75 through 79, 80 through 85, and older than 85. Nonsurvivors were also compared with survivors. Student's *t* test and analysis of variance were used to test statistical differences between groups of patients.

Results

The 76 nonsurvivors (4.9% mortality rate) had a lower mean age than the 1,491 survivors (Table 2). Nonsurvivors had a 3.8% lesser mean DRG weight index, but they had a 95.4% greater LOS, an 83.7% greater number of diagnoses, a 37.1% greater number of procedures, and a 56.3% greater severity of illness compared with survivors. Mean total hospital cost per patient was 159.2% greater for nonsurvivors compared with survivors; hospital cost per day was 94.6% greater. Nonsurvivors generated a $21,412 deficit per patient under DRG payment compared with a $6,119 surplus per patient for survivors. Emergency admissions and blood requirements were higher for nonsurvivors compared with survivors. The greatest number of deaths occurred during the first week of the hospital stay or during hospitalization lasting 31 through 60 days (Fig 1). The mean hospital cost per day for nonsurvivors, however, generally dropped as the LOS increased (Fig 2).

There were some significant differences in resource characteristics for nonsurvivors by the LOS (Table 3). Mean age and mean DRG weight index per patient did not differ significantly by LOS group. However, total hospital cost per patient, losses under DRGs, and outliers increased as LOS increased. The only category of nonsurvivors that generated a surplus was that of patients who died within seven days of admission to the hospital.

Route of admission (emergency versus nonemergency) was usually predictive of the level of aggregate resource consumption (Table 4). Patients admitted on an emergency basis who died tended to have a slightly shorter LOS, a similar number of diagnoses, a comparable severity of illness, and lower hospital costs per day compared with patients admitted on a nonemergency basis who died. Financial risk, as measured by mean total hospital cost per patient, losses under DRGs, and outliers, was less for nonsurvivors admitted on an emergency basis. The percentage of admissions to the surgical intensive care unit was similar for emergency and nonemergency nonsurvivors.

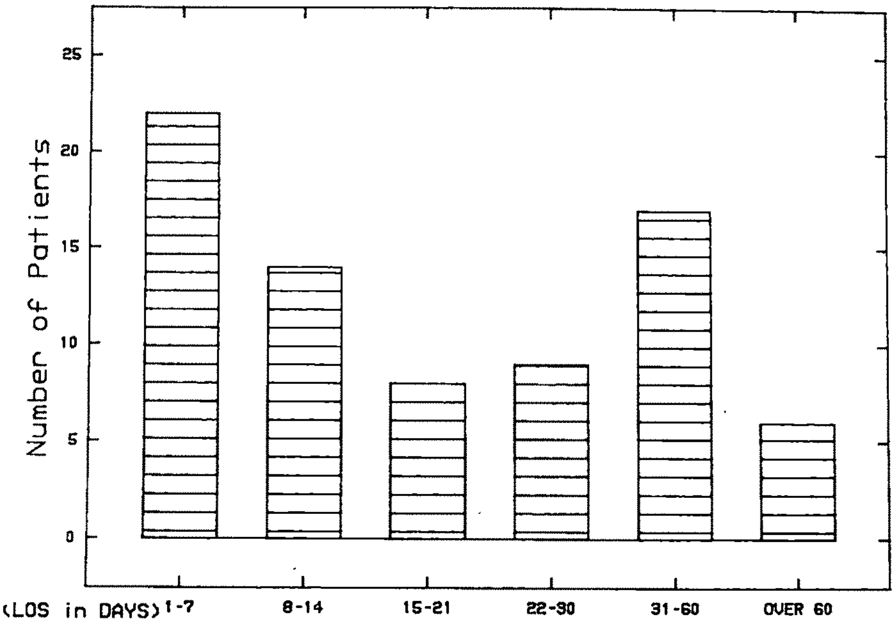

Fig 1. Number of deaths by length of stay (LOS) for cardiothoracic surgical nonsurvivors. The majority of deaths occurred during the first week in the hospital or during a stay of 31 through 60 days.

Nonsurvivors who changed clinical service had a much higher mean DRG weight index and a lower mean LOS compared with nonsurvivors who did not change clinical service (Table 5). Nonsurvivors who changed clinical service had a similar severity of illness and mean hospital cost per day compared with nonsurvivors who did not change clinical service. Nonsurvivors who were referred represented a much lower financial loss under DRGs than nonsurvivors who did not change clinical service. The reasons for these findings are multifactorial and will need further study.

Resource characteristics for nonsurvivors by age are shown in Table 6. The greatest percentage was in the 25 through 34-year-old age group (27.6%). The LOS per nonsurvivor was highest for patients 25 through 34 years of age (39.1 days). The highest mean DRG weight index for nonsurvivors was in patients 70 through 74 years of age (4.7693); there was usually no major variation in DRG weight index. The mean total hospital cost per nonsurvivor by age group ranged from $5,859 to $65,857; the highest was for nonsurvivors 25 through 34 years old. Five of eight age groups generated losses under DRG payment. The percentage of outliers ranged from 0% to 50.0%. Emergency admission was highest for nonsurvivors in the age group 35 through 44 years (100%).

Comment

The federal and state DRG prospective hospital payment systems are causing hospitals to merge clinical and financial data. After 5 years of the Medicare DRG program, it appears that the financial health of American hospitals

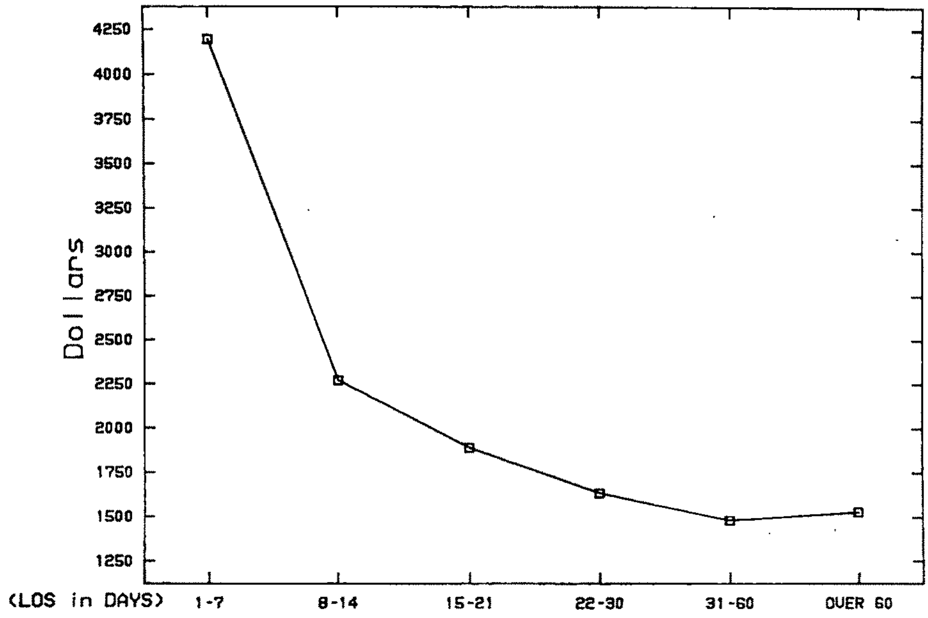

Fig 2. The mean hospital cost per day for cardiothoracic surgical patients who did not survive dropped as the length of stay (LOS) increased.

Table 3. Resource Consumption for Nonsurvivors by Length of Hospital Stay (Cardiothoracic Surgery)[a]

Length of Stay (days)	Age (yr)	DRG Weight Index	Hospital Costs	Profit/Loss[b]	Outliers (%)	Nonemergency Admissions (%)
1–7	47.0	4.4280	\$11,281[c]	\$12,636[c]	0[c]	81.8
8–14	53.4	4.3174	\$23,853	(\$493)	0[c]	57.2
15–21	55.0	4.4972	\$33,633	(\$9,367)[d]	0[c]	75.0
22–30	48.3	4.3073	\$41,400	(\$18,091)	0[d]	77.8
30–60	44.8	3.7147	\$65,612	(\$43,181)	82.4[c]	76.5
60+	52.3	4.5972	\$208,446[c]	(\$154,433)[c]	100.0[c]	83.3
All patients	49.1	4.2544	\$47,235	(\$21,412)	26.3	75.0

[a] Data are shown as the mean per patient. [b] This is the mean profit or loss per patient under DRG payment; data in parentheses equal loss. [c] Significance: $p < 0.01$ versus the mean. [d] Significance: $p < 0.05$ versus the mean.

DRG = diagnostic-related group.

has declined [8]. Despite much documentation regarding inequities in the federal program, there have been no major changes in DRGs implemented by either the Health Care Financing Administration or the US Congress. There are important health policy questions related to improving the equity of DRG hospital payment regarding cardiothoracic surgical deaths.

We analyzed hospital resource consumption for cardiothoracic surgical patients who died in the hospital. These patients consumed a disproportionate share of hospital resources compared with cardiothoracic surgical survivors; deaths also generated tremendous financial risk under DRG prospective pricing schemes. The greatest number of cardiothoracic surgical deaths occurred during the first week in the hospital. The mean hospital cost per day for nonsurvivors decreased as LOS per patient increased. Among nonsurvivors, only patients who died within 1 week of admission to the hospital generated a surplus under DRGs, whereas nonsurvivors with a very long LOS generated a financial risk to the hospital.

Our group [9] has taken an interest in route of admission (emergency versus nonemergency) and subsequent hospital cost. In general, a patient admitted on an emergency basis is more expensive than a patient admitted on a nonemergency basis per DRG. However, this was not the case for cardiothoracic surgical patients who died. Emergency cardiothoracic surgical patients who died tended to have a shorter LOS and represented less financial risk compared with nonemergency patients who died. Nonemergency patients who died, however, generated substantially more financial risk under DRGs compared with nonsurvivors admitted on an emergency basis. This

Table 4. Route of Admission (Emergency Versus Nonemergency) and Resource Consumption for Nonsurvivors (Cardiothoracic Surgery)[a]

Variable	Emergency (n = 19)	Nonemergency (n = 57)
Age (yr)	67.5[b]	43.0
DRG weight index	4.1823	4.2785
Length of hospital stay (days)	23.3	31.6
No. of diagnoses[c]	5.74	6.37
No. of procedures[c]	6.00	6.81
Total ICD-9-CM codes	11.74	13.18
Per patient hospital cost	\$34,202	\$51,580
Hospital cost per day	\$1,694	\$2,735
Profit/loss[d]	(\$9,796)	(\$25,284)
Outliers (%)	15.8	29.8
SICU admissions (%)	100	100
Blood transfused (%)	63.2[b]	94.7

[a] Data are shown as the mean per patient. [b] Significance: $p < 0.002$ versus nonemergency group. [c] This is the number of ICD-9-CM codes per patient. [d] This is the mean profit or loss per patient under DRG payment; data in parentheses equal loss.

DRG = diagnostic-related group; SICU = surgical intensive care unit.

Table 5. Change in Clinical Service and Resource Consumption for Nonsurvivors (Cardiothoracic Surgery)[a]

Variable	Referred (n = 28)	Nonreferred (n = 48)
Age (yr)	54.1	46.2
DRG weight index	5.0592[b]	3.7850
Length of hospital stay (days)	22.5	33.6
No. of diagnoses[c]	6.32	6.15
No. of procedures[c]	7.00	6.38
Total ICD-9-CM codes	13.32	12.52
Per patient hospital cost	\$40,033	\$51,436
Hospital cost per day	\$2,651	\$2,372
Profit/loss[d]	(\$10,900)	(\$27,544)
SICU admission (%)	100	100
Blood transfused (%)	96.4	81.3
Emergency admissions (%)	17.9	29.2

[a] Data are shown as the mean per patient. [b] Significance: $p < 0.001$ versus nonreferred group. [c] This is the number of ICD-9-CM codes per patient. [d] This is the mean profit or loss per patient under DRG payment; data in parentheses equal loss.

DRG = diagnostic-related group; SICU = surgical intensive care unit.

Table 6. Resource Consumption by Age for Nonsurvivors (Cardiothoracic Surgery)[a]

Age (yr)	Admission (%)	Length of Hospital Stay (days)	DRG Weight Index	Total Hospital Cost	Profit/ Loss[b]	Outliers (%)	Emergency Admissions (%)
25–34	27.6	39.1	3.8861	$65,857	($40,516)	28.6	0.0
35–44	1.3	3.0	3.6579	$5,859	$14,174	0.0	100[c]
45–54	5.3	29.0	3.8925	$43,056	($20,198)	50.0	25.0
55–64	13.2	31.0	4.2660	$51,373	($24,853)	40.0	20.0
65–69	14.5	10.5	4.0820	$17,953	$4,310	9.1	36.4
70–74	25.0	36.9	4.7693	$56,277	($26,487)	26.3	36.8
75–79	10.5	20.6	4.3956	$26,993	($2,812)	25.0	50.0
80–85	2.6	6.0[c]	4.5777	$16,181	$8,492	0.0	0.0
All patients	100	29.5	4.2544	$47,235	($21,412)	26.3	25.0

[a] Where applicable, data are shown as the mean per patient. [b] This is the mean profit or loss per patient under DRG payment; data in parentheses equal loss [c] Significance: $p < 0.05$ versus the mean.

is an unusual finding and contradicts the greater resource utilization of cardiothoracic surgical emergency admissions in general. One possible explanation is that nonsurvivors admitted on an emergency basis experience a rapid death (and hence lower cost) compared with nonsurvivors admitted on a nonemergency basis. Further study of the reasons for these findings is needed.

Patients who changed clinical service during hospitalization (ie, were referred to the cardiothoracic surgical service) and who died had lower total hospital costs and represented less financial risk under DRG pricing schemes compared with nonsurvivors who did not change clinical service; the reasons for this are likely complex and multifactorial. There were also some differences in resource consumption by age.

We have outlined characteristics for cardiothoracic surgical patients using the framework of the DRG classification scheme. This retrospective study is limited by constraints regarding risk stratification of cardiothoracic surgical patients. Our study, for example, could not ascertain when either higher cost or poorer outcome could have been avoided for these patients, or whether treatments were appropriate. Our group and others [10, 11], however, have suggested that surgical patients who die generate financial risk under DRGs and that some modification of the current DRG system along the lines of outcome for some groups of surgical patients should be considered. The health policy options regarding further modification of DRGs are complex; research has suggested that equity in DRG payment could be improved by stratifying DRGs by severity of illness, outcome, or complications and comorbidities [1]. The Health Care Financing Administration has proposed no major changes in DRGs, however, as of 1988 [2]. Hospitals may attempt to identify patients who represent potential cardiothoracic surgical deaths. It is possible to identify higher-risk patients, and thus patients representing a greater cost, before admission to the hospital and perhaps exclude them from care.

Health care finance and policy are undergoing rapid and dynamic change. Also, increasing interest has begun to focus on mortality data. There is a growing trend in the health services research community to study methods to use mortality data as a proxy or screen for quality of care. It is also possible that a link will be established for certain outcome measures and hospital or physician payment. Surgeons must now enter the arena of surgical health policy and economics. It is likely that in the future, changes in payment for cardiothoracic surgical services will increasingly affect access to and quality of cardiothoracic surgical services.

In conclusion, after 5 years of the federal DRG hospital payment program, there have been no major changes to the system implemented by the Congress. This study analyzed a large group of cardiothoracic surgical nonsurvivors with reference to hospital resource consumption. These nonsurvivors generated much greater resource consumption per DRG compared with survivors; increasing LOS for nonsurvivors was associated with increasing financial risk under DRGs. Eventual nonsurvivors admitted on a nonemergency basis generated greater financial risk compared with eventual nonsurvivors admitted on an emergency basis. Patients who were referred to the cardiothoracic surgical service from another clinical service and died generated (on average) lower resource consumption than those who were not referred and died.

This study supports previous suggestions that there are payment inequities in DRGs vis-à-vis cardiothoracic surgical nonsurvivors. It demonstrates that factors predictive of greater hospital resource utilization for cardiothoracic surgical patients who die—increasing LOS, nonemergency admission, and admission directly to the cardiothoracic surgical service—should perhaps be considered strongly in restructuring third-party hospital reimbursement policies.

We are indebted to Jonathan Goldstein, MPA, for data computation and to Christina Weiss for the preparation of the manuscript.

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REVIEW OF RECENT BOOKS

Brain Injury and Protection During Heart Surgery
Edited by Mark Hilberman
Norwell, MA, Kluwer Academic Publishers, 1987
173 pp, illustrated, $58.50

Reviewed by Carlos E. Moreno-Cabral, MD

An area of continued interest to the professionals involved in cardiac surgery with the use of extracorporeal circulation is the subject of *Brain Injury and Protection During Heart Surgery*. The selected group of contributors includes investigators with extensive background in this field. Although the majority of the contributors are anesthesiologists, cardiac surgeons, psychiatrists, and perfusionists have also contributed.

Being a compact book, this nine-chapter volume covers the topic extensively and is well referenced with a total of over 500 citations.

The first chapter serves as an introduction to the subject and also explains the basic improvements made in the past several years to decrease the incidence of cerebral complications after cardiopulmonary bypass (CPB). This is followed by chapters on low-flow, low-pressure CPB techniques and results, autoregulation of cerebral blood flow during CPB, and acid-base management during CPB with emphasis on the important role of carbon dioxide tension regulation. Separate chapters on microembolization and macroembolization are included. In both chapters, the sources of embolization and ways to prevent them are thoroughly discussed. It is made clear that elimination of embolization (both micro and macro) represents the major factor in reducing central nervous system complications after CPB. A controversial issue discussed in the chapter on macroembolization is the use of high-dose barbiturates for cerebral protection during CPB. The claim that "this therapeutic modality is indicated in patients undergoing valve replacements, resection of left ventricular aneurysms and other operations requiring opening of a cardiac chamber, and perhaps, for patients requiring other high risk procedures" seems somewhat excessive in view of the limited number of clinical studies available and the low incidence of cerebral injury even in those "high risk" patients. A comprehensive account of the current ways of assessing cerebral injury in cardiac surgical patients is the subject of another chapter. The chapter on perfusion techniques for CPB is in itself a well-presented contribution, but many concepts well covered in other chapters are repeated.

Whereas the book is well written, illustrated, and edited throughout, perhaps the highlight is represented by the concluding chapter on hypothermic circulatory arrest.

Despite the minor criticisms, this book represents a valuable contribution and is recommended as basic reading for all people directly involved in the care of the cardiac surgical patient, in particular anesthesiologists, surgeons, and perfusionists.

Stanford, California

True Thymic Hyperplasia: A Clinicopathological Study

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In this report, we describe the clinicopathological features of 4 patients with true thymic hyperplasia. This controversial thymic lesion has only recently been defined as a variable, often massive enlargement of the thymus characterized by a nearly normal microscopic structure. Our study of 4 patients and review of the literature indicate that true thymic hyperplasia has a well-defined clinicopathological profile: prevalence in children or young male patients, absence of associated autoimmune diseases, and often presence of respiratory distress or peripheral blood lymphocytosis, or both. True thymic hyperplasia should be considered in the differential diagnosis of anterior mediastinal masses in children and young adolescents.

(Ann Thorac Surg 1989;47:741–5)

Pathological enlargement of the thymus is due in most instances either to neoplasms of epithelial and nonepithelial origin or to hyperplastic conditions [1, 2]. In childhood, the most frequent cause of an anterior mediastinal mass is lymphoproliferative syndrome; thymic epithelial tumors are rare [3]. Two types of thymic hyperplasia have been described: lymphoid or follicular hyperplasia, often associated with myasthenia gravis [4] and histologically characterized by the presence of lymphoid follicles with activated germinal centers, and true thymic hyperplasia (TTH), characterized by variable and often massive enlargement of the thymus with a nearly normal histological appearance and absence of lymphoid follicles. The latter condition is rare; very few cases fulfilling the diagnostic criteria have been reported [5–10].

In the present study, we describe the clinicopathological features of 4 patients with TTH to contribute to a further and better understanding of this rare pathological condition.

Material and Methods

Clinical data on the 4 patients are summarized in Table 1.

Patient 1

An asymptomatic 16-year-old boy was admitted after a chest roentgenogram showed a mass in the anterior mediastinum (Fig 1). Chest tomography confirmed the finding. Physical examination, laboratory blood tests, pulmonary function tests, electrocardiogram (ECG), and electromyogram were within normal limits. The clinical preoperative diagnosis was thymoma. Through a left posterolateral thoracotomy, an ovoid, well-encapsulated anterior mediastinal mass with a diameter of 13 cm and a weight of 250 g was removed. The postoperative course was uneventful, and the patient is in good health 12 years after operation.

Patient 2

An asymptomatic, healthy 12-year-old boy was admitted when a chest roentgenogram showed mediastinal widening. Physical examination was normal. Chest roentgenography, chest tomography, and computed tomography demonstrated the presence of a mass in the anterior mediastinum between the innominate vein and the undersurface of the sternum. Laboratory blood tests, pulmonary function tests, ECG, and electromyogram were normal. The anterior mediastinum was approached through a partial median sternotomy from the jugular notch to the angle of Louis. A discoid mass with a diameter of 7.5 cm and a weight of 120 g was excised. The postoperative course was uneventful, and the patient is in good health 7 years after operation.

Patient 3

A 14-year-old boy was admitted with complaints of dyspnea. A diagnosis of cardiomegaly had been made 4 years previously in another hospital on the basis of chest roentgenography. Dyspnea had been attributed to this condition. A computed tomograph scan of the chest showed a large anterior mediastinal mass. The patient was referred to our institution with the diagnosis of thymolipoma. At admission (Fig 2), the patient was mildly dyspneic; pulmonary function tests revealed moderate reduction of vital capacity. The ECG was normal. Through a median sternotomy, a bulky mass weighing 850 g was excised. Both pleural cavities were entered to remove the lesion, which extended to both sides of the mediastinum, causing atelectasis of the left lower lobe and compression of the right middle lobe. Full reexpansion of the lungs was obtained, and the postoperative period was uneventful. The patient has been asymptomatic since 1980 and is in good health.

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Table 1. Clinical Features of 4 Patients With True Thymic Hyperplasia

Patient No.	Age (yr)	Sex	Thymus Weight (g)	Peripheral Blood	Symptoms
1	16	M	230	Normal	Absent
2	12	M	120	Normal	Mild dyspnea
3	14	M	840	Not determined	Dyspnea
4	5	M	950	Lymphocytosis	Dyspnea

Patient 4

A boy was first evaluated for dyspnea when he was 3 years old. At the age of 4 years, he was admitted to a hospital in a foreign country for evaluation of the dyspnea. A large mediastinal mass compressing the left lung and occupying most of the left hemithorax was discovered. The patient was taken to the operating room for biopsy and resection. Through a median sternotomy, multiple biopsy specimens were taken, but the procedure was discontinued for unknown reasons. The postoperative course was complicated by wound infection and osteomyelitis of the sternum.

The patient was referred to our institution in August 1987 at the age of 5 years with a diagnosis of "thymic hyperplasia." On admission he complained of mild dyspnea and chest pain; blood gas analysis showed a partial pressure of oxygen of 78 mm Hg, partial pressure of carbon dioxide of 45 mm Hg, and an acid-base balance within normal limits. Blood cell counts showed leukocytosis (white blood cell count, 24,800/μL) with absolute lymphocytosis (lymphocytes, 81%; neutrophils, 14.2%; monocytes, 2.8%; eosinophils, 2%). The ECG and blood pressure were normal. Physical examination revealed diminished breath sounds over the left chest. Chest roentgenography (Fig 3A), tomography, and computed tomography (Fig 3B) demonstrated a large anterior mediastinal mass occupying the left hemithorax and part of the right hemithorax. Electromyography was normal.

A median sternotomy was avoided because of previous sternal infection. The left hemithorax was approached through a standard lateral thoracotomy in the fifth interspace. The incision was later extended over the midline, and the sternum was horizontally transected up to the right parasternal line to remove the right edge of the tumor. A bulky, well-encapsulated mass weighing 950 g was excised. The patient was taken to the intensive care unit, and ventilatory support was started; extubation was accomplished on the third postoperative day, and there were no further respiratory complications. The hypoplastic left lung did not fully reexpand after removal of the mass. A small apical space was present when the patient was discharged in good general condition and fully asymptomatic 1 month after operation.

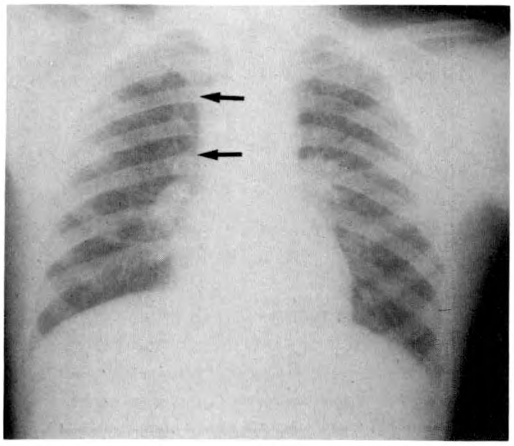

Fig 1. (Patient 1.) Posteroanterior chest roentgenogram. The arrows show the right edge of the mass modifying the mediastinal profile.

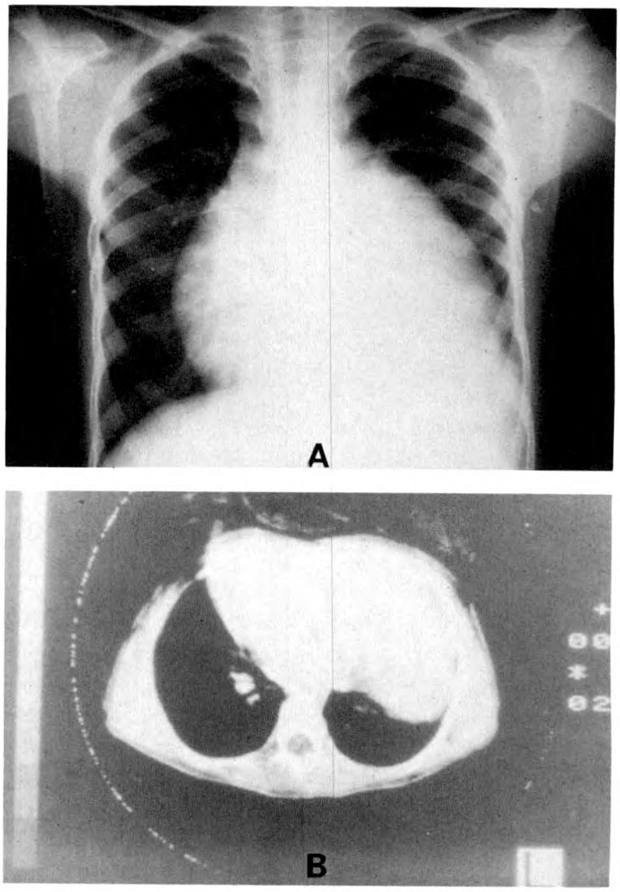

Fig 2. (Patient 3.) (A) Posteroanterior chest roentgenogram. Massive enlargement of the cardiac silhouette was misinterpreted as cardiomegaly. (B) Computed tomographic scan showing the presence of an anterior mediastinal mass with parenchymatous density.

Pathological Findings

The typical bilobate shape of the thymus was not recognizable in the first 3 patients, whereas in the fourth patient, two enlarged thymic lobes were still present. All the lesions were well circumscribed, encapsulated, grey yellow in color, and regularly lobulated. Histologically all patients had a structure composed of numerous lobules with well-defined cortical and medullary areas (Fig 4A, B), thus resembling the normal thymus. However, some

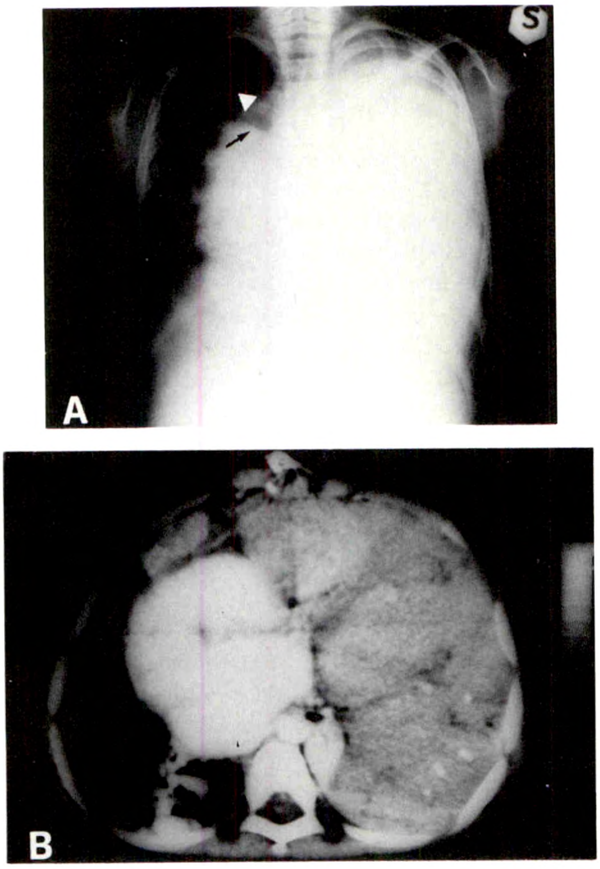

Fig 3. (Patient 4.) (A) Posteroanterior chest roentgenogram. The arrows show the carina and the left main bronchus displaced in the right hemithorax. (B) Computed tomographic scan of the thorax showing a bulky mass occupying the entire left hemithorax and displacing the mediastinum to the right.

peculiar morphological traits are noteworthy. In patient 1, each lobule was completely surrounded by fibrovascular septa. In patients 2 and 4, prevalence of the medullary area was noted with several Hassall's bodies present even within the cortex (Fig 4C). In patients 3 and 4, mature fatty tissue was observed between the fibrous septa and the thymic parenchyma. This finding indicated an early lipomatous involution (Fig 4D). In each patient, the final diagnosis was true thymic hyperplasia.

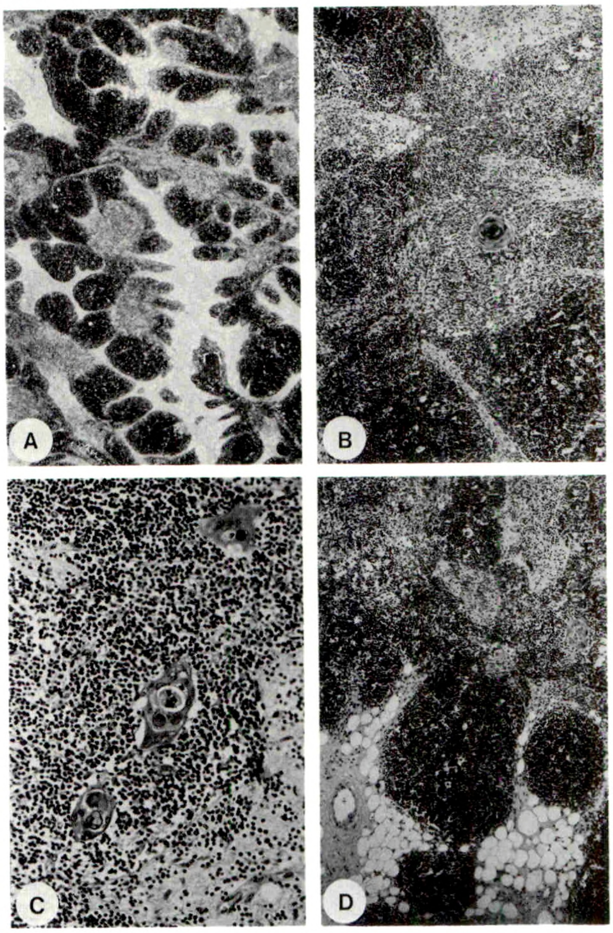

Fig. 4. (A) Histologically normal thymic lobules are present. (×40 before 45% reduction.) (B) Well-defined cortical and medullary areas are shown. A large Hassall's corpuscle is visible (×100 before 45% reduction.) (C) Some small Hassall's corpuscles are present in the cortex. (×250 before 45% reduction.) (D) A moderate lipomatous involution of the thymic parenchyma is shown. (×100 before 45% reduction.) (All, H&E.)

Comment

For a long time, TTH has been a controversial pathological condition [1]. Within the last 12 years, a few well-documented cases of TTH with massive enlargement of the thymus have been published [5–10]. From the present study and our review of the 7 cases reported in the

Table 2. Clinical Features of Massive True Thymic Hyperplasia in the Literature

Reference	Age	Sex	Thymus Weight (g)	Peripheral Blood	Symptoms
Moriber Katz et al [5]	7 mo	M	224	Lymphocytosis	Hepatomegaly
O'Shea et al [6]	12 mo	M	420	Lymphocytosis	Dyspnea
Rasore-Quintino et al [7]	4 yr	F	800	Lymphocytosis	Enteritis
Lee et al [8]	22 mo	F	550	Not determined	Absent
Lack [9]	11 yr	M	324	Normal	Mild dyspnea
	14 yr	M	490	Normal	Absent
Arliss et al [10]	15 yr	M	680	Lymphocytosis	Chronic hepatitis

literature, it appears that TTH is a disease that mostly affects male children or young adolescents (Table 2). Clinically, TTH is characterized by the following: (1) asymptomatic enlargement of the anterior mediastinum (55% of patients) or symptomatic mass (45%) causing compressive problems such as respiratory distress; (2) lymphocytosis (45% of patients); (3) absence of associated autoimmune disorders such as myasthenia gravis; and (4) benign process. True thymic hyperplasia can be a small mass and generally asymptomatic, or it can be a large mass causing massive mediastinal enlargement. One or both hemithoraces can be involved and cause dyspnea, chest pain, or both.

Because these patients rarely have a preoperative diagnosis, the operative approach should be chosen primarily to allow complete access to the anterior mediastinum. In 1 of our 2 patients with massive TTH, the lesion was easily excised through a longitudinal median sternotomy. In the second, it was approached through a standard left thoracotomy with a transverse sternotomy, which proved to be very suitable for controlling the left costovertebral and posterior costophrenic sinuses occupied by the mass.

Macroscopically the thymus is massively enlarged compared with the thymus in controls of the same age and even with the upper limit of normal thymus weight (about 50 g) [11, 12]. The microscopic appearance of TTH is that of a nearly normal thymus without lymphoid follicles with activated germinal centers.

True thymic hyperplasia must be differentiated from other pathological conditions such as thymoma of the cortical type with areas of medullary differentiation ("organoid" thymoma) [13], lymphoid follicular hyperplasia of the thymus, thymolipoma, and mediastinal lymphoblastic lymphoma. Clinically, TTH and thymoma can be distinguished by the more aggressive behavior of the latter, which can cause symptoms related to invasion such as pain and superior vena caval syndrome rather than compressive symptomatology. Histologically, in the "organoid" thymoma, medullary differentiation is represented by small and ill-defined foci present in neoplastic tissue composed mostly of a cortexlike parenchyma. The differential diagnosis of TTH is crucial because thymomas, although very rare in young patients, often have aggressive biological and clinical features [3].

In lymphoid follicular hyperplasia, the thymus can be moderately enlarged. The most characteristic histological feature of this condition is the presence of lymphoid follicles with activated germinal centers, which are always absent in TTH. Furthermore, lymphoid or follicular hyperplasia is the most common thymic lesion associated with myasthenia gravis [4], which has never been reported in patients affected by TTH.

Thymolipoma is another cause of massive thymic enlargement in young patients. This peculiar thymic condition sometimes displays a bilobulate appearance on computed tomographic sections and can confuse the differential diagnosis. Histologically there is a prevalence of mature fatty tissue [14, 15]. In TTH, a moderate lipomatous involution can be present; however, the main component is normal hyperplastic thymic tissue.

Lymphoblastic lymphoma is one of the most frequent causes of mediastinal enlargement in childhood. The differential diagnosis of TTH can be difficult on small biopsy specimens obtained by needle biopsy or fine-needle aspiration, whereas it is obvious on gross surgical specimens.

Finally, other peculiar thymic enlargements have been described in association with certain treated conditions such as Hodgkin's disease [16], some childhood tumors [17], primary hypothyroidism [18], and Beckwith-Wiedemann syndrome [19]. This phenomenon, defined as "thymic rebound" and related to known causes, must be differentiated from idiopathic TTH.

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Notice From the Southern Thoracic Surgical Association

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Phoenician Golf and Tennis Resort, Scottsdale, AZ, November 9–11, 1989. There will be a $155 registration fee for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 9, 1989. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1989, to Bradley M. Rodgers, MD, Program Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract submission form. These forms may be obtained from the Association's office. All slides used during the presentation must be 35 mm. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1989 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1989, and forwarded to Hooshang Bolooki, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601.

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Akinetic Versus Dyskinetic Left Ventricular Aneurysms Diagnosed by Gated Scintigraphy: Difference in Surgical Outcome

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Forty-one patients selected for left ventricular aneurysm resection and coronary artery bypass grafting were studied by gated radionuclide ventriculography and right heart catheterization before and after operation to establish whether the presence of paradoxically systolic expansion, as defined by radionuclide ventriculography, influenced the surgical outcome. Patients with systolic paradoxically moving left ventricular aneurysms (n = 28) improved their functional classification (New York Heart Association) ($p < 0.01$) and exercise tolerance (watt-minutes) ($p < 0.001$) compared with preoperative values, in contrast to the patients with akinetic aneurysms (n = 13), whose status remained unchanged. Left ventricular ejection fraction at rest ($p < 0.001$) and exercise ($p < 0.0001$) improved along with a significant reduction in left ventricular end-diastolic ($p < 0.002$) and end-systolic volume indices ($p < 0.001$) among the patients with paradoxical left ventricular aneurysms versus no change in the akinetic group. In a multivariate analysis of different preoperative variables, the presence of dyskinesia was found to be the only independent predictor of a favorable surgical outcome ($p < 0.004$). In conclusion, the presence of dyskinesia represents an important marker of the outcome after aneurysmectomy.

(Ann Thorac Surg 1989;47:746–51)

Patients with left ventricular (LV) aneurysm represent a heterogenous group in terms of impairment of LV function. Resection of an LV aneurysm can result in symptomatic improvement, whereas objective LV improvement has been more difficult to demonstrate, and deterioration does occasionally occur [1, 2].

Previous studies have focused on the quality of the contractile segment as the most important factor predicting the operative result in patients with LV aneurysm [3, 4], but there is controversy about this in the literature [5]. Paradoxical expansion of an aneurysm in contrast to an akinetic aneurysm has been suggested as a possible predictor of surgical outcome [6–8].

The purpose of this prospective study was to compare LV performance and exercise tolerance in patients treated surgically for akinetic versus dyskinetic LV aneurysms in an effort to assess the clinical importance of paradoxical movement in regard to surgical outcome.

Material and Methods

Patients

From September 1984 to January 1986, a consecutive series of 50 patients selected for LV aneurysmectomy and coronary artery bypass grafting on the basis of contrast left ventriculography and coronary angiography were studied. Six patients died postoperatively, 3 of whom were judged dyskinetic and 3, akinetic on radionuclide ventriculography. Except for 1 patient from each group, all patients who died were treated with additional surgical procedures: mitral valve replacement (1), encircling endocardial ventriculotomy (2), or endocardial resection (2). In 3 patients, the radionuclide ventriculographic study was incomplete. Thus, the present study comprises 41 patients ranging in age from 30 to 67 years (mean age, 54 ± 8 years) studied both before and after operation (mean follow-up, 10 ± 4 months).

Methods

Preoperatively all patients underwent left and right heart catheterization with ventriculography. An LV aneurysm was considered present when an akinetic or dyskinetic segment clearly demarcated from the contractile section was found on the ventriculogram [9]. Selective coronary angiography was performed in multiple projections, and obstruction of more than 75% of the lumen was considered severe. Right heart catheterization with cardiac output measurements by the method of Fick and right ventriculography were done in all patients both preoperatively and postoperatively using the same techniques.

Before and after operation, radionuclide ventriculography at rest was performed in all patients in the supine position in the anterior, left anterior oblique, and left lateral projection using a General Electric scintillation camera with an all-purpose collimator [10]. Red blood cells labeled with 900 mBq of technetium 99m–labeled pertechnetate were used as the tracer.

Supine exercise was performed on a bicycle ergometer starting at a work load of 25 W and increasing every three minutes until one or more of the following criteria were met: angina pectoris, heavy dyspnea, falling systolic blood pressure, severe arrhythmia, and exhaustion. The

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level of work load achieved was expressed as watt-minutes (watts × minutes exercised). The exercise study was obtained in the left anterior oblique position. Thirty-two patients were studied during exercise preoperatively and 34, postoperatively. The remaining patients were precluded from this because of disabling symptoms either before or after operation. Twenty-seven patients were studied both before and after aneurysmectomy.

Left ventricular ejection fraction (LVEF) was calculated using background-subtracted systolic and diastolic LV contours drawn semiautomatically. Peak filling rates were derived from the time–activity curves and expressed as end-diastolic volumes per second. Fourier analysis (mathematical analysis of the time–activity curve) was performed on the smoothed data [7]. Phase and amplitude values were derived from the first harmonic of the Fourier transform using the R wave of the electrocardiogram as the reference point for all phase angles calculated. The phase image was displayed by applying a color scale that extended through the entire spectrum of phase values (0 through 360 degrees). Paradoxical wall motion pattern of an aneurysm was considered present when the phase angle difference between normally contracting areas and aneurysmal areas of the left ventricle extended more than 90 degrees with increased count activity in systole similar to the left atrium [7]. All aneurysms without these signs of paradoxical wall motion were considered akinetic LV aneurysms.

Left ventricular end-diastolic and end-systolic volume indices (LVEDVI, LVESVI) were calculated from nuclear-derived LVEF and the Fick-derived stroke volume index (SVI) by the following formulas: LVEDVI = SVI/LVEF and LVESVI = LVEDVI − SVI [11].

Surgical Procedures

Standard cardiopulmonary bypass with moderate hypothermia was established. Moderate systemic hypothermia to 28°C was used. The aneurysmectomy was performed using standard techniques; a narrow rim of fibrous tissue was left for suturing the LV defect, which was closed with mattress sutures buttressed with Teflon felt. Left ventricular aneurysms less than 3 × 3 cm were considered small and all others, medium or large.

Eleven patients with akinetic LV aneurysms received coronary artery bypass grafts versus 15 patients with dyskinetic aneurysms. The distal venous anastomoses were performed during crystalloid cardioplegia and proximal anastomoses were performed during rewarming. Encircling endocardial ventriculotomy was performed in 7 patients (2 in the akinetic group and 5 in the dyskinetic group [not significant]). All patients had sustained the myocardial infarction or infarctions more than 6 months before operation.

Statistical Analysis

All data are expressed as the mean ± one standard deviation. Univariate analysis was done in the case of discrete variables by Fisher's exact test and in the case of continuous variables, by the Mann-Whitney test. Preoperative and postoperative comparisons were analyzed according to the centered signed rank test for paired comparison [12]. A multiple linear regression analysis using a manual backward-elimination procedure was used to assess independent variables of favorable surgical outcome [13].

Results

Baseline Characteristics

Based on preoperative radionuclide ventriculography, 13 patients had an akinetic LV aneurysm (group A) and the remaining 28, a dyskinetic (paradoxical wall motion) LV aneurysm (group B). The groups were not significantly different in terms of functional classification, symptoms, and cardiac medication apart from digitoxin, which was more commonly used in group B (Table 1). Angina pectoris was the dominant symptom and indication for operation. Catheterization data and distribution of severe coronary artery obstruction and number of bypass grafts were similar in the groups. However, LVEF was significantly lower in the dyskinetic group at rest and during

Table 1. Clinical, Catheterization, and Operative Data on Patients With Akinetic (Group A) and Dyskinetic Left Ventricular Aneurysm (Group B)[a]

Variable	Group A (n = 13)	Group B (n = 28)	*p* Value
NYHA class	2.8 ± 0.8	3.10 ± 0.7	NS
Symptoms			
Heart failure	3 (23)	9 (32)	NS
Angina pectoris	8 (62)	15 (54)	NS
Ventricular tachycardia	2 (15)	4 (14)	NS
Cardioactive drugs			
Digitoxin	2 (15)	15 (54)	<0.04
Diuretics	4 (31)	6 (21)	NS
β-blockers	10 (77)	15 (54)	NS
Isosorbide dinitrate	9 (69)	15 (54)	NS
Calcium antagonists	4 (31)	9 (32)	NS
Antiarrhythmic agent	2 (15)	6 (21)	NS
ACE inhibitors	1 (8)	4 (14)	NS
Catheterization			
LVEDP (mm Hg)	18 ± 5	20 ± 9	NS
CI (L/min/m^2) (Fick)	2.8 ± 0.6	2.5 ± 0.5	NS
Vessels diseased			
One	3 (23)	9 (32)	NS
Two	2 (15)	8 (29)	NS
Three	8 (62)	11 (39)	NS
Operation			
No. of grafts	2.09 ± 0.5	1.86 ± 0.7	NS
Medium/large aneurysm	7 (54)	23 (82)	NS
Small aneurysm	6 (46)	5 (18)	NS

[a] Where applicable, data are shown as the mean ± one standard deviation. Numbers in parentheses are percentages.

ACE = angiotensin-converting enzyme; CI = cardiac index; LVEDP = left ventricular end-diastolic pressure; NS = not significant; NYHA = New York Heart Association.

Table 2. Preoperative and Postoperative Results in Patients With Akinetic (Group A) and Dyskinetic (Group B) Left Ventricular Aneurysm[a]

Variable	Before	After	p Value	No. of Patients
Group A				
LVEF, rest (%)	35 ± 9	33 ± 11	NS	13
LVEF, exercise (%)	35 ± 8	39 ± 9	NS	9
SVI (mL/m²)	44 ± 9	37 ± 9	<0.004	13
LVEDVI (mL/m²)	134 ± 36	124 ± 30	NS	13
LVESVI (mL/m²)	90 ± 33	87 ± 31	NS	13
PFR (EDV/s)	1.5 ± 0.5	1.7 ± 0.3	<0.05	13
Group B				
LVEF, rest (%)	27 ± 10[b]	34 ± 9	<0.001	28
LVEF, exercise (%)	27 ± 9[b]	37 ± 9	<0.0001	18
SVI (mL/m²)	39 ± 11	38 ± 11	NS	28
LVEDVI (mL/m²)	164 ± 83	115 ± 28	<0.002	28
LVESVI (mL/m²)	125 ± 83	77 ± 24	<0.001	28
PFR (EDV/s)	1.3 ± 0.5	1.5 ± 0.4	<0.05	28

[a] Data are shown as the mean ± one standard deviation. [b] Significance: $p < 0.05$ compared with group A.

EDV = end-diastolic volume; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NS = not significant; PFR = peak filling rate; SVI = stroke volume index.

exercise ($p < 0.05$), although there was much overlapping between the groups (Table 2; Fig 1). The preoperative differences in end-diastolic and end-systolic volume indices between the groups did not reach significance.

Operative Results

New York Heart Association functional class in group B changed from 3.1 ± 0.7 to 2.4 ± 0.8 ($p < 0.01$) versus 2.8 ± 0.5 to 2.4 ± 0.8 in group A (not significant). Work load and double product (heart rate × systolic blood pressure) achieved after operation showed significant improvement in the dyskinetic group, whereas these did not reach significance in the akinetic group (Table 3). Patients with dyskinetic LV aneurysms increased LVEF both at rest and during exercise in contrast to the patients with akinetic LV aneurysms (see Table 2). The absolute increase in mean LVEF at rest was 6.5% ± 8% with 95% confidence intervals of +3% to +10% in group B versus a decrease in mean LVEF of −2.3% ± 8% ($p < 0.001$) and 95% confidence intervals of −7% to −2% in group A (Fig 2).

End-diastolic and end-systolic volume indices decreased significantly in the dyskinetic group; no such significant change was seen in the akinetic patients. The

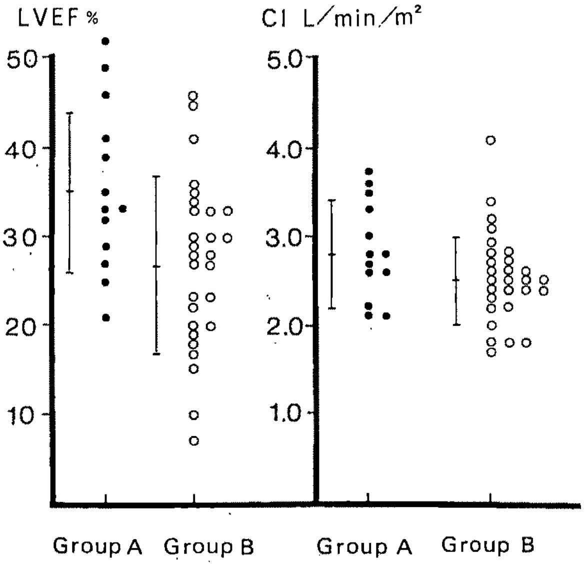

Fig 1. Distribution of left ventricular ejection fraction (LVEF) and cardiac index (CI) at rest in patients with akinetic (group A) and dyskinetic (group B) left ventricular aneurysm before operation. There is great overlap between the groups.

Table 3. Double Product and Work Load During Exercise in Patients With Akinetic (Group A) and Dyskinetic (Group B) Left Ventricular Aneurysm Before and After Operation[a]

Variable	Before	After	p Value
Group A[b]			
Double product[c]	15,859 ± 3,544	18,024 ± 3,479	NS
Work load (W-min)	470 ± 257	505 ± 426	NS
Group B (n = 22)			
Double product[c]	14,554 ± 3,417	20,330 ± 5,879	<0.002
Work load (W-min)	435 ± 284	822 ± 438	<0.001

[a] Data are shown as the mean ± one standard deviation. [b] Data represent measurements from 10 patients before operation and 12 patients after operation. [c] Double product = heart rate × systolic blood pressure.

NS = not significant.

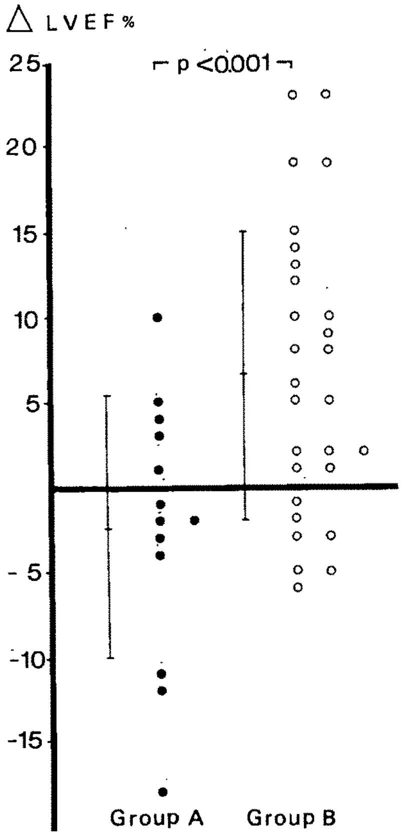

Fig 2. Absolute increase or decrease (Δ) in left ventricular ejection fraction (LVEF) at rest before and after operation in patients with akinetic (group A) and dyskinetic (group B) left ventricular aneurysm.

stroke volume index remained unchanged among the dyskinetic patients, whereas a significant reduction was observed in group A after operation. The peak filling rate increased significantly in both groups after operation. Pulmonary capillary wedge pressure was 14 ± 9 mm Hg before and 14 ± 10 mm Hg after operation in the dyskinetic group; an increase from 9 ± 6 mm Hg to 16 ± 8 mm Hg ($p < 0.003$) was observed in the akinetic group.

A significant linear correlation between decrease in end-diastolic volume and increase in LVEF was found in the patients with dyskinetic LV aneurysm ($r = 0.53$, $p < 0.005$), whereas no such relationship was found in the akinetic group. Comparing the change in EFs and volume indices in one group with the change in the other showed a significant difference in the increase in EF at rest ($p < 0.001$) and in the decrease in end-systolic volume indices ($p < 0.05$). The changes in end-diastolic volume indices and LVEF during exercise were not significantly different between the groups.

Multiple linear regression analysis estimated a least squares regression equation between a dependent variable equal to the difference between LVEF at rest after and LVEF at rest before operation, with LV end-diastolic volume index, LV end-systolic volume index, stroke volume index, cardiac index, and a dichotomized variable of grouping (dyskinetic versus akinetic) as the independent variables. The backward elimination procedures pinpointed grouping as the sole indicator of improved surgical outcome ($p < 0.004$).

Comment

Paradoxical expansion of an aneurysm has led to the hypothesis that a part of the stroke volume is being ejected into the aneurysm, thus creating volume stress [7], but few prospective studies have addressed the clinical importance of this. The terms *dyskinesia* and *akinesia* are difficult to quantify, and studies [8, 14] have shown obvious limitations in the detection of these wall motion disturbances by cineangiography. Fourier phase analysis, however, seems particularly well suited for detection of dyskinesia in patients with LV aneurysm because it has the advantage of being independent of geometry [6–8]. Because not all patients with LV aneurysm benefit from aneurysm operation [1, 2] and because the procedure carries a higher risk than coronary artery bypass grafting alone [8], it is of great importance to try to identify patients who really benefit from surgical intervention for an aneurysm.

The present study showed consistent improvement in functional classification, exercise tolerance, and cardiac performance in the patients with a dyskinetic LV aneurysm in contrast to those in the akinetic group. This suggests that the paradoxically systolic expansion diagnosed by radionuclide ventriculography may prove valuable in selecting patients suitable for aneurysm resection. The clinical study of Yiannikas and co-workers [7] claimed that the extent of paradoxical movement in the Fourier phase and amplitude analysis is most powerful in predicting improvement in LV function after aneurysm resection. Ormerod and colleagues [8] found that the extent of increase in LVEF was related to the size of the paradoxical segment resected.

These observations seemingly contrast with the report of Parmley and associates [15], who have previously shown in vitro that chronic fibrous aneurysms appear to produce their primary mechanical disadvantage by a loss of contractile tissue and that the systolic paradox is negligible. However, aneurysms are often made up of a mixture of scar tissue and viable myocardium or of thin scar tissue that produces a mechanical disadvantage by a combination of paradoxical expansion and loss of effective contraction [16].

Patients with dyskinetic LV aneurysms had more severely compromised LV function preoperatively than those in the akinetic group. Surprisingly, patients with the best preoperative LV performance benefited least from operation. The same observation was made by Stephens and colleagues [2], who explained it by a favorable shift in the Frank-Starling relation after operation on patients with poorer LV performance. It appears that the more expansive the aneurysm, the greater the volume stress placed on the contractile segment [7]. Thus, systolic paradoxical expansion aggravating the volume overload may be an important and additional explanation for the more impaired LV function in patients with dyskinetic LV aneurysms compared with patients with akinetic LV aneurysm. In accordance with this, we observed high end-diastolic volume indices in group B. The presence of dyskinesia can thus be regarded as an important marker for the severity of an aneurysm leading to volume overload, LV dilation, and impaired cardiac performance.

End-diastolic volumes were significantly reduced in the dyskinetic group. Operation on patients in the akinetic group, however, failed to reduce the end-diastolic volumes significantly. The reason for this may be either poorly demarcated scarring [8] making adequate resection difficult or postoperative dilation. Patients with a decrease in stroke volume probably had no beneficial effect from aneurysmectomy. Improvement in ventricular function as a result of bypass grafting of ischemic myocardium may have been counteracted by injury to surrounding viable myocardium during operation as proposed by Sesto and associates [17]. The lack of improvement in the akinetic group suggests that the measured improvement in the dyskinetic group was the result of aneurysm resection rather than coronary artery grafting.

End-diastolic volume is an important determinant of surgical outcome in patients with LV aneurysm because the goal of aneurysmectomy is to reduce end-diastolic volume and thereby regional wall tension [9]. Accordingly, a correlation was found between the decrease in end-diastolic volume and the increase in LVEF among the patients with dyskinetic LV aneurysm after operation. Furthermore, it seems logical that patients with large aneurysms and large end-diastolic volumes should experience greater hemodynamic changes than others. In theory, therefore, one might assume that the surgical outcome depends mainly on preoperative end-diastolic volume and not on the presence or absence of dyskinesia. However, multivariate analysis did not show LV end-diastolic volume index to be an independent predictor of surgical outcome. This finding is in agreement with the report of Yiannikas and co-workers [7], who suggested that even patients with large aneurysms had no benefit from aneurysmectomy when the aneurysms were nondistensible. Thus, assessment of the size of the aneurysm alone is probably inadequate when the aim of operation is to improve LV function.

The end-systolic volumes paralleled the end-diastolic volumes, with a significant decrease in the dyskinetic group compared with no change in the akinetic group. In 1987, White and associates [18] reported end-systolic volume as the major determinant of survival after myocardial infarction. They suggested increased wall stress leading to increased myocardial oxygen demand to be the most important risk factor for ventricular fibrillation, which was the cause of death in 70% of the patients who died. Whether these findings can be applied to patients with LV aneurysm remains to be studied.

Exercise tolerance was improved postoperatively in the patients with dyskinetic aneurysm. This finding is important because the functional capacity during exercise may not necessarily correlate with the degree of LV dysfunction [19]. The increase achieved in double product and work load represents additional information about circulatory function. Thus, a reduction in wall tension and oxygen demand [20] along with an increase in oxygen supply by revascularization has relieved symptoms as well as provided patients a better exercise performance.

Some limitations of this study have to be considered. The disparity in size between the groups and the differences in baseline hemodynamics make the statistics difficult to interpret. Furthermore, because of the relatively small number of patients in the akinetic group, some reservations have to be considered. However, the consistency in the operative results together with the results of the multivariate analysis supports the assumption that patients with dyskinetic LV aneurysm benefit more from aneurysm resection than those with akinetic aneurysms. Individual variations within the respective groups were observed, with some patients in group A whose condition slightly improved and some patients in group B whose condition became worse. A different finding would have been surprising in a consecutive series of patients with such a heterogeneity in symptoms, anatomy, LV performance, hemodynamics, and overlap between the groups. Moreover, patients in both groups were threatened by a long list of possible mechanisms of perioperative myocardial damage such as technical failures, inadequate myocardial protection, and myocardial reperfusion.

In conclusion, functional classification, exercise tolerance, and LV performance improved after aneurysm resection in patients with radionuclide ventriculography–detected dyskinetic LV aneurysms in contrast to patients with akinetic aneurysms. Patients who are candidates for aneurysm resection and who are seen with distinct paradoxical wall motion are more likely to benefit from LV aneurysm resection than others.

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Use of an Intraaortic Balloon Pump as a Pneumatic Ventricular Assist Device Controller

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Using a circulatory analogue, we investigated sequentially the performance of a dedicated ventricular assist device driver and an intraaortic balloon pump when driving a pneumatic ventricular assist device. Each drive device was compared under identical pumping conditions at rates of 40 to 120 cycles/min against two resistances. Our preliminary study showed that a modified intraaortic balloon pump could drive a pneumatic ventricular assist device as effectively as its dedicated driver. The necessary modifications to and possible further development of the intraaortic balloon in this role are discussed.

(Ann Thorac Surg 1989;47:752–5)

Pulsatile ventricular assist devices (VADs) have been in limited clinical use for several years. These devices are employed in some centers in the management of cardiogenic shock after operation [1, 2] or myocardial infarction [3] when other supportive measures have failed. Ventricular assist devices also have a role in the support of a failing heart as a bridge to cardiac transplantation [4, 5].

In the United Kingdom, clinical experience with pulsatile VADs is limited to a very small number of patients. A major constraint on the further application of this support technique is the cost of the necessary equipment. A typical VAD system consists of a dedicated driver, costing around $35,000, and the VAD components themselves (the VAD shell, valves, blood sac, and conduits), costing $20,000 per patient. Few cardiac surgical centers in the United Kingdom could contemplate the regular use of such expensive devices, despite their possible lifesaving role [6].

Our group considered the possibility of using an intraaortic balloon pump (IABP) to power a pneumatic VAD. Most cardiac surgical centers have access to several IABPs. If VAD driving with an IABP were feasible, it could reduce the capital cost of introducing a VAD program by eliminating the need to purchase a costly dedicated VAD driver.

In pneumatic and control terms, there are many similarities between the function of both drive devices. We therefore set out to investigate the feasibility of pumping a VAD with an IABP in a simple circulatory analogue, and compared its performance with that of a dedicated VAD controller.

Material and Methods

A two-chambered circulatory loop capable of emulating the flows and pressures seen in the systemic circulation in humans was constructed (Fig 1). A Pierce-Donachy pneumatic VAD (Thoratec, Berkeley, CA) was connected either to a dedicated VAD driver (Thoratec) or to a modified IABP (Datascope, Paramus, NJ). The IABP (Datascope System 80) was modified as follows. The slave chamber was removed and the exhaust system altered to permit either the dumping of exhaust gas directly to the atmosphere or the application of up to 30 mm Hg vacuum. This modification necessitated disconnection of the IABP "low vacuum" alarm.

With the VAD connected to the circulatory loop, two experiments were performed.

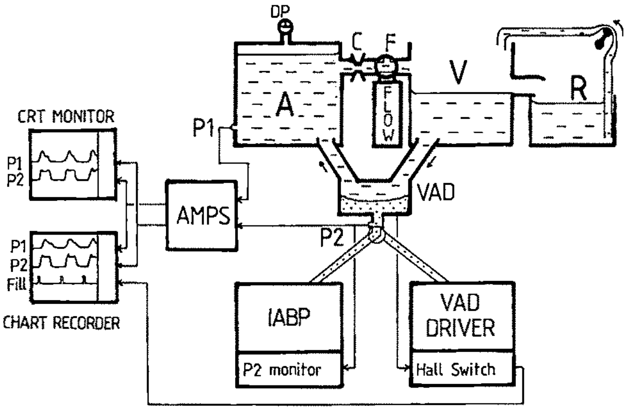

Fig 1. Components of the circulatory analogue and its connection to the ventricular assist device (VAD). *(*A = *arterial chamber;* C = *interchangeable constriction;* CRT = *cathode ray tube;* DP = *deairing point;* F = *flow measurement point;* IABP = *intraaortic balloon pump;* P1 = *"arterial" pressure transducer;* P2 = *driveline pressure transducer;* R = *reservoir;* V = *venous chamber.)*

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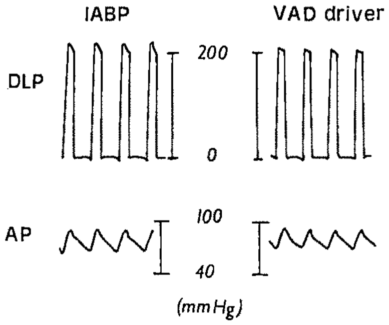

Fig 2. Typical "arterial" (AP) and driveline pressure (DLP) traces of both devices while operating at a rate of 80 cycles/min. (IABP = intraaortic balloon pump; VAD = ventricular assist device.)

Experiment 1

Loop conditions were determined with resistances consisting of double-tapered constrictions with minimum diameters of 0.178 cm^2 (R1) and 0.045 cm^2 (R2) while compliance was held constant. The two drive devices were alternated at trigger rates of 40 to 120 cycles/min in steps of 10 cycles/min. Driveline pressures delivered to the VAD were adjusted to maintain a difference of less than 5 mm Hg at the midsystolic point between the two drive devices for each paired comparison. A constant "venous" pressure was maintained, and the timing controls were then adjusted to achieve maximal VAD output while maintaining identical systolic and diastolic time intervals with both drive devices. "Arterial" and driveline pressures were recorded (Fig 2), and pump outputs were measured volumetrically.

Experiment 2

Experiment 1 was repeated with the IABP driver under R1 conditions as described except that a minimum systolic interval of 20% was permitted. Controls on the Thoratec VAD driver limit the minimum allowable systolic interval to 30%.

Table 1. Mean "Arterial" Pressures Generated in Experiment 1 Under R1 and R2 Conditions[a]

Rate (cycles/min)	Mean "Arterial" Pressure (mm Hg) R1	R2
40	38	40
50	49	51
60	60	67
70	73	82
80	79	80
90	85	93
100	86	92
120	79	86

[a] The R1 and R2 conditions were resistances of double-tapered constrictions with minimum diameters of 0.178 cm^2 and 0.045 cm^2, respectively; compliance was constant.

Results

Experiment 1

Performance of the system was identical with both drive units under the conditions in this experiment. Figure 3 illustrates the flow rates achieved with the IABP and VAD drive units. Mean pressures generated within the loop are shown in Table 1. At rates higher than 60 cycles/min under R1 conditions and higher than 50 cycles/min under R2 conditions, the stroke volume of the VAD was reduced (reflected by the flattening of the flow rate curves in Figure 3).

Experiment 2

The IABP achieved optimal stroke volumes at higher pump rates with systolic intervals shortened to 20%, resulting in a diastolic filling interval of 80% of each cycle (Fig 4). This was not possible with the Thoratec driver, which permits reduction of the systolic time interval to only 30%, thus limiting the maximum diastolic filling time to 70% of a cycle.

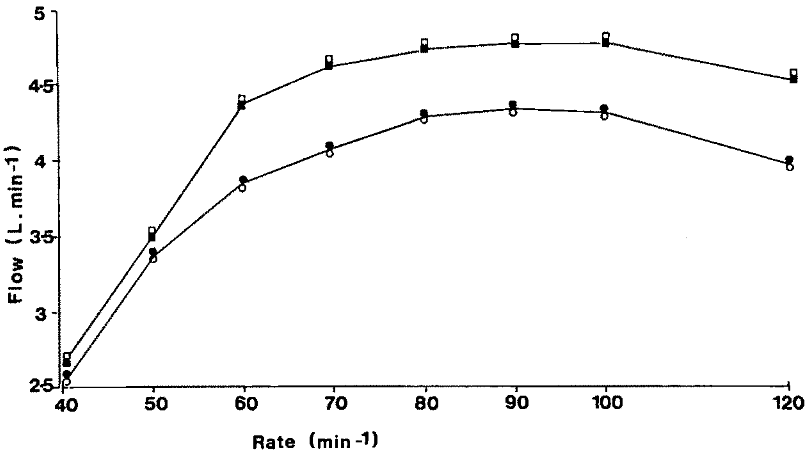

Fig 3. Flows obtained with the drive devices between rates of 40 to 120 cycles/min (min^{-1}) in experiment 1. (□ = intraaortic balloon pump at R1; ○ = intraaortic balloon pump at R2; ■ = ventricular assist device at R1; ● = ventricular assist device at R2.)

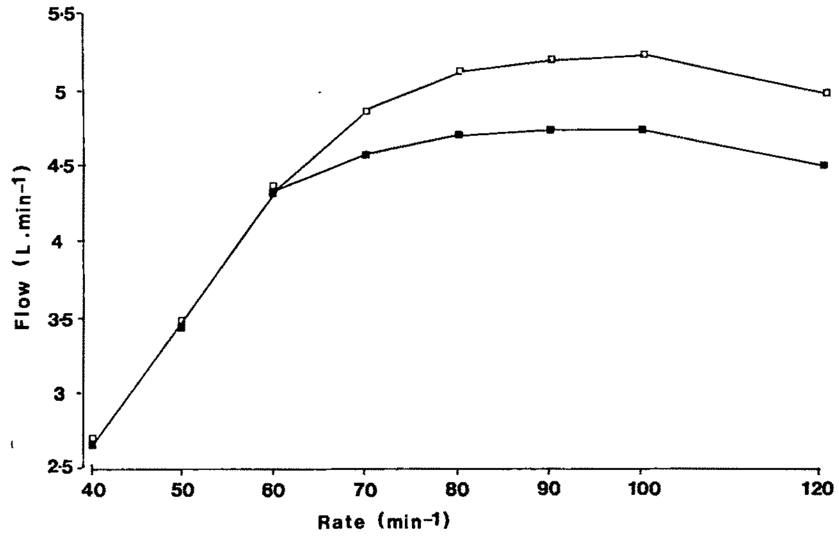

Fig 4. Flows achieved with the intraaortic balloon pump in experiment 2. (■ = systolic interval of 30%; □ = systolic interval of 20%.)

Comment

It appears from our study that a modified IABP can successfully drive a pneumatic VAD.

Under conditions presented to the VAD in our study, VAD stroke volume fell at higher rates (see Figs 3, 4). Our observations during the study lead us to the conclusion that this was partly due to relatively slow filling of the VAD during pump diastole, as increasing the diastolic interval to 80% in experiment 2 led to higher flows. In clinical practice, VADs are likely to be run at rates that would allow longer diastolic filling times to occur. Also, application of a small amount of vacuum during diastole may improve VAD filling.

Our exclusion of the slave or safety chamber from the pneumatic circuit of the IABP merits comment. In the intended role of an IABP, the slave chamber is essential, as it isolates the patient to some extent from the gas compressor and permits use of a fixed volume of carbon dioxide or helium to fill the secondary (ie, patient) circuit. However, there is no advantage in retaining the slave chamber when pumping VADs, and indeed the Pierce-Donachy and similar VADs isolate the drive gas from the blood sac with a double envelope, thereby effectively providing a built-in safety layer. A leak in either layer leads to reduced VAD function, and is usually very obvious on visual inspection.

Our initial experience while setting up this study demonstrated that adequate control of a VAD using an IABP in which the standard-volume or a large-volume (100-mL) slave chamber was retained was difficult to achieve. There could also be problems refilling a slave gas compartment, as clearly it is not desirable to interrupt VAD pumping for longer than a few seconds, and except in those IABP models with "auto-fill" facilities, longer interruptions would be likely. We are, however, aware that a VAD driving system utilizing a "slave" arrangement is currently under development.

Further development of IABPs as VAD drivers will lead to expansion of control and alarm systems to provide for the specific needs of VAD driving. Facilities for monitoring the driveline pressure waveform [7, 8] and VAD stroke volume [9] are highly desirable. Alarm systems tailored to VAD driving requirements and fail-safe internal and external triggering will be essential for long-term use of an IABP in the VAD driving mode. We have constructed an additional control unit incorporating some of these features; it is currently being tested.

In conclusion, a minimally modified IABP functioned satisfactorily as a VAD driver in a circulatory loop. We have conducted animal studies using the support system for periods of longer than 36 hours, and the results are encouraging. While we await the results of a more detailed evaluation, we believe that an IABP can be used as a backup for a dedicated pneumatic VAD driver. In the future, combined IABP and VAD drive devices may prove to be cost-effective replacements for the older separate devices.

We thank the staff of the Heart-Lung and Medical Electronics Departments of Brompton Hospital for their cooperation during the study. M. Self of Datascope BV, Holland, and Datascope Medical Ltd, UK, provided advice and arranged partial funding of the project.

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REVIEW OF RECENT BOOKS

Manual of Postoperative Management in Adult Cardiac Surgery

By Carlos E. Moreno-Cabral, R. Scott Mitchell, and D. Craig Miller
Baltimore, Williams & Wilkins, 1988
102 pp, illustrated, $21.95

Reviewed by Karl E. Karlson, MD

This pocket-size book describes in detail the principles and practice of postoperative care of cardiac patients in the Stanford University Medical Center. The manual is meant for the instruction and guidance of medical students, junior surgical residents, and intensive care unit nurses. In addition to a brief text (63 pages), there are copies of numerous forms and routine doctor's order sheets that are used at Stanford. Various forms used by nurses, including Kardexes for sets of postoperative orders, are illustrated. There is a table of infusion rates for cardiovascular drugs. Antiarrhythmic drugs are tabulated with route of administration, dose, indications, and toxicity given. A table pertaining to drug therapy in renal failure lists over 100 drugs, with the half-life and dosage adjustments necessary.

Brief explanations of cardiopulmonary bypass and common cardiac operations are given, together with pertinent pathophysiology, to form a basis for postoperative routines. The rationale for treatment of postoperative problems is discussed in sections devoted to bleeding, hypotension, low cardiac output, arrhythmias, pacing, hypertension, fever, postpericardiotomy syndrome, respiratory insufficiency, renal failure, and neurological complications.

This is a comprehensive, yet short and concise, handbook which is a quick guide for intensive care unit care. The tables in the appendix summarize most of the current drugs for handy reference.

Providence, Rhode Island

Different Responses of Coronary Artery and Internal Mammary Artery Bypass Grafts to Ergonovine and Nitroglycerin in Variant Angina

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The dynamic responses of a coronary artery and an internal mammary artery (IMA) graft to pharmacological intervention were examined by arteriography in 5 patients with variant angina who had undergone coronary artery bypass grafting with an in situ IMA to the left anterior descending coronary artery. Preoperative electrocardiographic findings included elevated ST segments in chest leads during attacks of angina, and all patients had severe fixed lesions in addition to marked spasm of the left anterior descending coronary artery after the administration of ergonovine maleate. Postoperatively with ergonovine stimulation, complete occlusion or marked subtotal narrowing was again observed at the primary fixed lesion in the proximal portion of the left anterior descending coronary artery, but the IMA graft and the coronary artery distal to the anastomotic site maintained satisfactory patency with no further occurrence of anginal pain or ST segment elevation. By computer-assisted graphic analysis, which allows highly reproducible measurements of vascular internal diameters, the diameter of the IMA showed only small changes under ergonovine (p = not significant) or nitroglycerin ($p < 0.05$) stimulation in contrast to the marked vascular reactivity of the coronary artery ($p < 0.05$ and <0.01, respectively). These findings indicate that the IMA graft is unresponsive to ergonovine at least in the amount required to produce coronary artery spasm in patients with variant angina and fixed lesions. The IMA graft appears to function well from a clinical and pharmacological viewpoint in patients with variant angina.

(Ann Thorac Surg 1989;47:756–60)

The variant form of angina pectoris with elevation of the ST segment during attacks caused by coronary artery spasm is frequently provoked by administration of ergonovine maleate [1–3]. We performed coronary artery bypass grafting by anastomosing the left internal mammary artery (IMA) to the left anterior descending coronary artery (LAD) in 5 patients with variant angina in whom major fixed lesions associated with coronary artery spasm were observed on arteriograms during ergonovine and nitroglycerin loading. Postoperatively, repeat coronary arteriography with pharmacological intervention demonstrated a difference in vascular reactivities to pharmacological stimulation between the IMA graft and the coronary artery. This report describes a favorable characteristic of IMA grafts used in patients with variant angina associated with structural fixed coronary stenosis.

Material and Methods

Five patients with variant angina associated with major fixed lesions underwent myocardial revascularization with an in situ IMA graft to the LAD. Postoperative angiography with pharmacological intervention was performed to evaluate the comparative vascular reactivities of the coronary artery and the IMA graft. Preoperative electrocardiographic findings included elevated ST segments in chest leads during spontaneous anginal attacks, a finding compatible with a diagnosis of variant angina. In all patients, preoperative stimulation with ergonovine yielded a positive response in the LAD (the occurrence of angina, coronary artery spasm, and ST segment elevation on the electrocardiogram).

Patient profiles are shown in Table 1. There were 4 men and 1 woman ranging in age from 35 to 65 years (mean age, 51 ± 11 years). In all patients, angina usually occurred soon after waking up in the morning and was accompanied by reversible ST segment elevation in chest leads. None of the patients had had a previous myocardial infarction.

Preoperative coronary arteriography demonstrated that coronary artery spasms occurring after the administration of ergonovine produced total or subtotal occlusion of the LAD. In addition, the administration of nitroglycerin revealed a mean fixed stenosis in the LAD that was 94% ± 5% of the luminal diameter. All patients had a structural LAD lesion, and 4 of the 5 patients also had other diseased vessels.

The mean number of grafts was 2.0 ± 0.7 per patient. The left IMA was anastomosed to the LAD with the use of cold diltiazem potassium–blood cardioplegic solution [4] to prevent perioperative coronary artery spasm in all patients. Saphenous vein grafts were also employed in patients with multivessel disease.

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Table 1. Summary of Patient Data

Patient No.	Age (yr)	Sex	History of MI	Angina at Rest	ST Segment Elevation on Attack	Coronary Artery Disease (≥75%)	No. of Grafts	Perioperative MI	Postoperative Angina	Postoperative Follow-up
1	49	M	No	Yes	Yes	LAD	1 (LIMA–LAD)	No	No	2 yr 6 mo
2	35	F	No	Yes	Yes	LAD, LMT	2 (LIMA–LAD, SVG–LCX)	No	No	2 yr 6 mo
3	65	M	No	Yes	Yes	LAD, LCX, RCA	3 (LIMA–LAD, SVG–RCA, SVG–LCX)	No	No	2 yr 4 mo
4	51	M	No	Yes	Yes	LAD, RCA	2 (LIMA–LAD, SVG–RCA)	No	No	1 yr 6 mo
5	55	M	No	Yes	Yes	LAD, LCX	2 (LIMA–LAD, SVG–LCX)	No	No	1 yr 4 mo
Mean	51 ± 11 yr						2.0 ± 0.7/patient			2.0 ± 0.6 yr

LAD = left anterior descending coronary artery; LCX = left circumflex artery; LIMA = left internal mammary artery; LMT = left main trunk; MI = myocardial infarction; RCA = right coronary artery; SVG = saphenous vein graft.

Coronary and graft arteriography with pharmacological stimulation was repeated 1 to 3 months (mean period, 1.2 ± 0.8 months) postoperatively. Informed consent was obtained from the patients. Medication was withdrawn 48 hours before the examination. Cineangiograms of the IMA graft were made by manual injection of the contrast material (5 to 6 mL) through an F7 or F8 catheter. We tried to control the pressure generated during injection as evenly as possible in each study.

First, control angiography was performed (ie, without drug administration). Then the examination was repeated during intravenous injection of ergonovine (0.2 to 0.4 mg) over a period of nine to 12 minutes and similarly during administration of nitroglycerin (0.5 mg). Responses of the LAD and IMA diameters to pharmacological stimulation were compared by computer-assisted graphic analysis, details of which have been reported elsewhere [5, 6].

Briefly, end-diastolic cineangiographic images were represented in a 256 × 256 pixel array and quantified at each pixel according to a maximum 64-grade luminescence scale with a model LA-4 image-analyzing system (Pias Co, Osaka, Japan). End-diastolic images were digitized, and edges of the vessels were determined according to the method described by Spears and associates [7], ie, by the first derivative of the densitometric gradient curve (count profile curve) along a line perpendicular to the vessels. The accuracy of this method has been examined in model studies [5, 6]. A significant correlation was observed between known and measured values of the diameters of several different types of wire ($r = +0.99$, $p < 0.001$).

Using this method, the diameters of the IMA and LAD were determined at three sites each (in the IMA just proximal to the IMA–LAD anastomosis and in the LAD, just distal to it), delineated by 30-degree right anterior oblique projections. Values were corrected for magnification using images of a Judkins catheter of known diameter. The differences were examined by a paired or unpaired Wilcoxon test and single-factor analysis of variance. Changes were considered significant at a p value of less than 0.05.

Results

Operative Results

There were no operative or late deaths, and no myocardial infarctions occurred early or late postoperatively. Follow-up ranged from 1 year 4 months to 2 years 6 months (mean follow-up, 2.0 ± 0.6 years). Postoperative management of all patients included prophylactic medication with oral isosorbide dinitrate (15 mg/day). There has been no recurrence of angina, and all of the patients are in New York Heart Association functional class I.

Graft Patency

The IMA–LAD anastomosis proved to be patent in all patients, but two of five saphenous vein grafts were occluded at the time of follow-up; however, no critically ischemic regions remained.

Arteriographic Findings With Ergonovine and Nitroglycerin Administration

With the administration of ergonovine, the primary fixed lesion in the proximal portion of the LAD became completely occluded in 3 of the 5 patients, and showed marked narrowing (99%) in the remaining 2 patients. However, the IMA maintained adequate perfusion to the area supplied by the distal LAD without the occurrence of angina or ST segment elevation on the electrocardiograms.

Figure 1 shows postoperative images of the IMA graft and the LAD in a patient (patient 4) with a 90% fixed stenosis in segment 6 (American Heart Association classification) of the LAD who exhibited complete occlusion during ergonovine loading preoperatively. In the control arteriogram, the IMA retrogradely supplied the proximal portion of the LAD. During ergonovine stimulation, however, the coronary arteries became slightly spastic, and

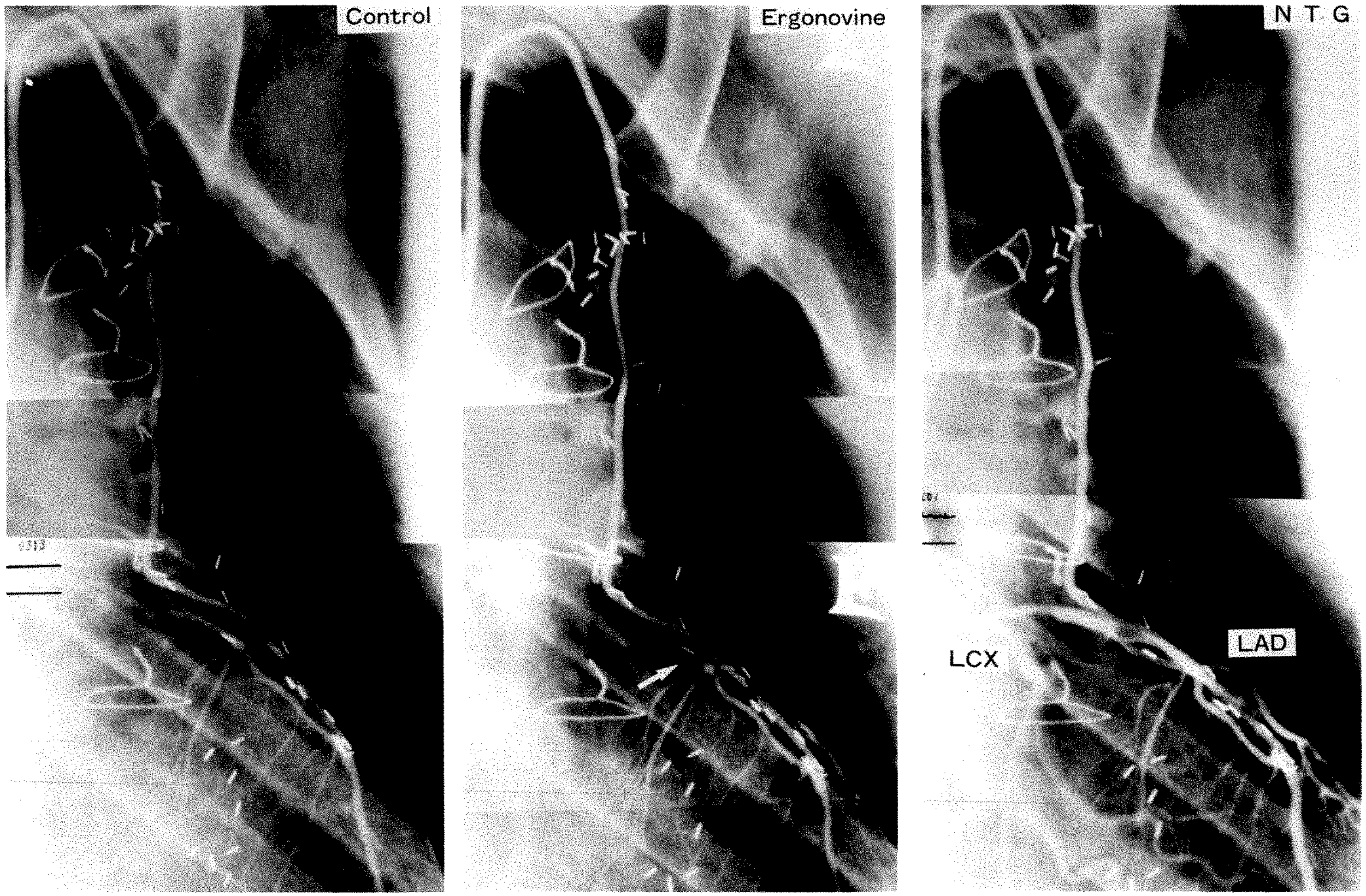

Fig 1. (Patient 4.) Postoperative graft angiograms of a 51-year-old man with variant angina associated with a 90% fixed stenosis in the left anterior descending coronary artery (LAD). *In the control angiogram, the internal mammary artery* (IMA) *graft filled the LAD anterogradely and retrogradely. When ergonovine maleate was given intravenously, the LAD became totally occluded at the stenotic portion* (white arrow), *but the IMA graft did not show a major change in diameter, and the distal LAD was well perfused through the IMA graft. After nitroglycerin* (NTG) *was administered intravenously, the LAD dilated markedly. The IMA graft showed less dilation and perfused even the left circumflex* (LCX) *system.*

Table 2. Measurements of Internal Vascular Diameters and Responsiveness to Pharmacological Intervention

Patient No.	Artery	Internal Diameter (mm) Control	Ergonovine	Nitroglycerin	Percent of Control Diameter (%) Control	Ergonovine	Nitroglycerin
1	IMA	2.07	2.28	2.48	100	110	120
	LAD	2.37	1.59	3.96	100	67	167
2	IMA	1.48	1.48	1.85	100	100	125
	LAD	1.78	1.30	3.12	100	73	175
3	IMA	2.10	1.95	2.10	100	93	100
	LAD	1.68	1.47	1.97	100	88	117
4	IMA	2.00	1.74	2.26	100	87	113
	LAD	2.00	1.61	2.66	100	81	133
5	IMA	1.98	1.98	2.38	100	100	120
	LAD	1.65	1.56	2.47	100	95	150
Mean[a]	IMA	1.93 ± 0.25	1.89 ± 0.30	2.21 ± 0.25	100 ± 0	98 ± 9[b,c]	116 ± 10[c]
	LAD	1.90 ± 0.30	1.51 ± 0.13	2.84 ± 0.75	100 ± 0	81 ± 11[b,d]	148 ± 24[d]

[a] Data are shown as the mean ± the standard deviation. [b] Significance: $p < 0.05$ versus other vessel; [c] Significance: $p < 0.05$ versus other pharmacological intervention (ergonovine vs nitroglycerin); [d] Significance: $p < 0.01$ versus other pharmacological intervention (ergonovine vs nitroglycerin)

IMA = internal mammary artery; LAD = left anterior descending coronary artery.

the LAD was completely occluded. In contrast, the IMA showed no notable changes in internal diameter and perfused the distal LAD region satisfactorily. With the administration of nitroglycerin, both the coronary artery and the IMA were dilated, and the IMA filled the entire LAD region as well as part of the region supplied by the circumflex artery.

Measurements of Internal Vascular Diameters and Responsiveness to Pharmacological Intervention

Mean internal diameters at control arteriography were as follows: IMA, 1.93 ± 0.25 mm, and LAD, 1.90 ± 0.30 mm (Table 2). The ratio between the two diameters was 1.06 ± 0.17. The diameter of the IMA was almost the same as that of the LAD on the control angiograms.

Changes in the internal diameter of the IMA and LAD during pharmacological stimulation were evaluated, and the results are shown in Table 2. Because the control diameter was different in each patient, comparison was made based on the percentage of the control angiographic value (100%). The LAD became spastic, and its diameter was reduced under ergonovine loading to 81% ± 11% of the control value. In contrast, the diameter of the IMA remained at 98% ± 9% of the control value, and its change was significantly smaller compared with that of the LAD ($p < 0.05$). With nitroglycerin, the LAD showed markedly significant dilation to 148% ± 24% of the control value ($p < 0.01$), whereas the IMA was much less significantly dilated to only 116% ± 10% of the control value ($p < 0.05$). The sequential changes in vascular diameter are shown in Figure 2.

Comment

The assessment of spasm and spasmogenicity of coronary arteries has been successfully accomplished by coronary arteriography with pharmacological intervention, which is apparently the only method currently available for evaluating dynamic vascular reactivity in humans [1–3, 8]. Manual injection of contrast material through a catheter can lead to variability in the filling of the arteries, thus resulting in somewhat unreliable vascular imaging. However, errors in the measurement of vascular diameters caused by angiographic variability in imaging appear to be smaller in comparative studies involving the same individual rather than different individuals. Therefore, percent changes in vessel diameter rather than actually measured calibers were used in Figure 2 to compare the

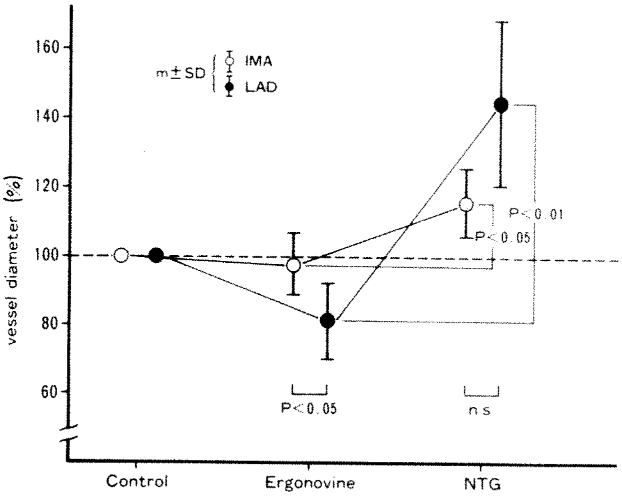

Fig 2. Percent of control angiographic diameters of the internal mammary artery (IMA) graft and the left anterior descending coronary artery (LAD) at the time of pharmacological intervention (the control angiographic value was considered to be 100%). The vascular reactivity in response to ergonovine maleate and nitroglycerin (NTG) was more significant in the LAD than in the IMA graft. (m±SD = mean ± standard deviation; ns = not significant.)

diameters of different arteries in different individuals. Visual evaluation of internal vascular diameters in cineangiographic images demonstrated poor reproducibility because of interobserver variations [5, 7]. With our method, which uses digital image processing of cinefilms [5, 6], we could accurately measure the internal vascular diameter. Our method also proved useful for evaluating changes in the vascular diameter during pharmacological stimulation.

Singh and Sosa [9] reported dilation of the coronary artery and the IMA graft after nitroglycerin administration. We quantitatively examined the responsiveness of the IMA graft and the LAD to ergonovine and nitroglycerin in 5 patients with variant angina who underwent coronary artery bypass grafting. The diameter of the LAD was reduced during ergonovine stimulation to approximately 80% of the control value, but that of the IMA remained almost unchanged. Moreover, with nitroglycerin stimulation, the LAD was dilated approximately 1.5 times the control value, whereas the IMA was dilated only about 1.2 times, the degree of dilation being significantly smaller. These findings suggest that although the IMA graft is viable [6, 9], it shows resistance to both ergonovine and nitroglycerin stimulation compared with the coronary artery.

According to Hackett and co-workers [8], ergonovine exerts a direct local effect on the coronary artery and causes coronary spasms by inducing localized arterial hyperreactivity. Yokoyama and colleagues [10] noted differences in the responsiveness to ergonovine between a systemic artery, such as the femoral artery, and the coronary artery in hyperlipidemic rabbits, and suggested that these differences were derived from differences in the receptor level. Although the difference in the responsiveness to ergonovine between the systemic and coronary arteries has not yet been sufficiently demonstrated in humans, our present study indicates at least a quantitative difference in response between the viable IMA graft and the coronary artery.

Spontaneous IMA graft spasm after coronary artery bypass grafting has been reported [11, 12]. The vascular response of the IMA grafts to ergonovine was not assessed in these patients, and the mechanism of IMA graft spasm may differ from that of the pharmacologically provoked spasm. However, it would appear to be very difficult to differentiate between IMA graft spasm and coronary artery spasm [13] in catastrophic perioperative events. In the present study, major IMA spasm could not be induced with ergonovine administered in the amount required to produce major coronary artery spasm in patients with variant angina. Thus, the mechanisms of occurrence of IMA graft spasm and coronary artery spasm may differ, at least in terms of dose requirements of vasoconstrictive drugs.

Although the number of patients is limited, our study has demonstrated an important physiological phenomenon in humans in regard to comparative vascular reactivities of the coronary artery and the IMA in response to ergonovine and nitroglycerin loading. We think the IMA graft can function well from a clinical and pharmacological viewpoint in patients with variant angina associated with fixed coronary lesions.

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Direct Tricuspid Closure Versus Atrial Partitioning in Fontan Operation for Complex Lesions

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Thirty-three patients with complex lesions undergoing the Fontan operation needed either direct tricuspid closure (group 1, 14 patients) or atrial partitioning (group 2, 19 patients). In group 1, the tricuspid patch was sutured to the annulus leaving the coronary sinus draining to the systemic venous atrium. In group 2, atrial partitioning was accomplished with either a Dacron or a polytetrafluoroethylene patch, leaving the coronary sinus draining to the pulmonary venous atrium. Intraoperative distention of the left side was used to check for residual defects. In group 1, complete heart block developed in 5 patients (36%) and patch disruption, in 4 patients (29%). There were 3 late deaths (21%), which were due to sudden death, sepsis caused by *Candida*, and liver failure. In group 2, no patient had heart block, and patch disruption developed in 1 patient (5%). There was 1 early death (5%) and 2 late deaths (11%), which were due to sepsis caused by *Candida* and renal failure. Our experience suggests that atrial partitioning is a better approach than direct tricuspid patch closure in patients with complex lesions undergoing the Fontan operation.

(Ann Thorac Surg 1989;47:761–4)

Since the use of the Fontan operation has been extended to more complex lesions other than tricuspid atresia, various ways of separating the atrial blood flow have evolved [1–6]. We initially used direct tricuspid closure [7] but switched to atrial partitioning after encountering problems of patch disruption and complete heart block. To determine whether atrial partitioning is a better approach than direct tricuspid valve closure, we reviewed our experience.

Material and Methods

Patient Population

From February 1980 to July 1988, 33 patients who underwent the Fontan operation in our institution needed either direct tricuspid closure (group 1) or atrial partitioning (group 2).

The 14 patients in group 1 underwent the Fontan operation between February 1980 and June 1986. Age ranged from 2 to 20 years (mean age, 10.7 years). The diagnoses were single ventricle, 8 patients; transposition of the great arteries with ventricular septal defect and hypoplastic right ventricle, 3; double-outlet right ventricle with hypoplastic right ventricle, 1 patient; double-outlet right ventricle with hypoplastic left ventricle, 1; and pulmonary atresia with intact ventricular septum, 1. Two patients had dextrocardia. One had congenital heart block.

Twenty palliative procedures had been done including seven Glenn shunts, three pulmonary artery bandings, nine systemic–pulmonary artery shunts (subclavian–pulmonary in 7 and Waterston-Cooley in 2), and one pacemaker implantation. In 1 patient with a single ventricle and pulmonary stenosis who had a Glenn shunt and simultaneous tricuspid valve closure at 9 months of age because of severe tricuspid insufficiency, heart block necessitating pacemaker implantation developed. The Fontan operation was done when the patient was 2 years of age. Three patients, all with pulmonary stenosis, (aged 5, 7, and 15 years) did not have prior surgical palliation. Systolic pulmonary artery pressure ranged from 13 to 55 mm Hg (mean, 23 mm Hg) and pulmonary vascular resistance, from 0.5 to 2.9 U/m^2. One patient with single ventricle {S,L,L} (based on Van Praagh's classification of malposition of the heart [8]) had a gradient of 80 mm Hg across a narrowed bulboventricular foramen.

The 19 patients in group 2 underwent the Fontan operation between November 1980 and July 1988. Although we changed to atrial partitioning in late 1986, 4 patients included in the study were operated on before that period. These 4 patients needed atrial partitioning because of mitral atresia (2), complete common atrioventricular canal with hypoplastic left ventricle (1), and suspected mitral stenosis (1). Age in the group ranged from 3 to 16 years (mean age, 8.3 years). The diagnoses were single ventricle, 6 patients; transposition of the great arteries with hypoplastic ventricle, 4; double-outlet right ventricle with hypoplastic left ventricle, 5; and common atrioventricular canal with hypoplastic ventricle, 4. Eleven patients had two adequate atrioventricular valves. Two patients had polysplenia, and 1 patient had asplenia. One patient had dextrocardia.

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Forty-two palliative surgical interventions had been done including 13 Glenn shunts, seven pulmonary artery bandings, 17 systemic–pulmonary artery shunts (subclavian–pulmonary artery in 15, and Waterston-Cooley in 2), four atrial septectomies, and one ligation of a persistent left superior vena cava prior to a Glenn shunt. Only 2 patients, both with pulmonary stenosis, (aged 5 and 16 years) did not have prior surgical palliation. Systolic pulmonary artery pressure ranged from 11 to 40 mm Hg (mean, 21 mm Hg) and pulmonary vascular resistance, 0.2 to 3.1 U/m^2.

Surgical Technique

Because the technique for the Fontan operation has been widely reported, we will only touch on some important points. For cardiopulmonary bypass, the venae cavae were individually cannulated through the right atrium as far apart as possible to allow a generous atrial flap for the atriopulmonary connection. In patients with a Glenn shunt, only the inferior vena cava was cannulated. A ventricular apical sump and moderate hypothermia (25° to 30°C) were used. The operation was carried out during spontaneous ventricular fibrillation. The aorta was cross-clamped and blood cardioplegia given only if the heart continued to beat, to minimize the possibility of air embolism.

In group 1, either a Dacron or polytetrafluoroethylene patch was used for the tricuspid closure. The patch was sutured to the tricuspid annulus using continuous sutures in 3 patients and interrupted sutures in 11 patients (Fig 1A). The coronary sinus was left draining to the systemic venous atrium.

In group 2, either a Dacron (2 patients) or polytetrafluoroethylene patch (17 patients) was used for the atrial septation (Fig 1B). In the presence of an intact atrial septum, an atrial septal defect was created. Continuous suturing, reinforced with four to six interrupted sutures, was used. A redundant patch was avoided, especially in patients with mitral atresia or stenosis so as not to impair pulmonary venous flow to the tricuspid valve. After the patch was placed, the ventricular sump was clamped to distend the left atrium and uncover any leak in the patch. The coronary sinus was left draining to the pulmonary venous atrium.

Atriopulmonary connections were accomplished in 30 patients with direct anastomosis using the atrial flap complemented anteriorly with either a Dacron or Gore-Tex patch [9, 10]. The Glenn shunts were not disturbed. Early in the series, valved conduits were used in 3 patients.

Results

Early Results

GROUP 1. There were no early deaths (less than 1 month postoperatively).

Complete heart block necessitating permanent cardiac pacemaker implantation developed in 5 patients (36%). One patient subsequently resumed atrioventricular conduction.

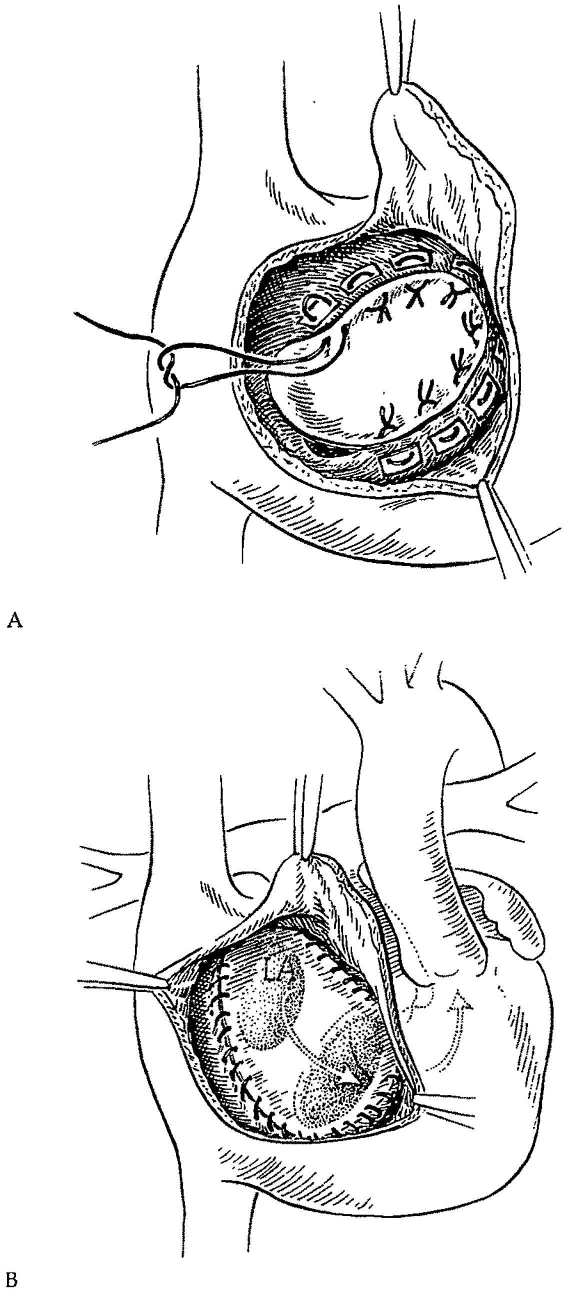

Fig 1. (A) Direct tricuspid closure. Sutures are placed in the annulus, and the coronary sinus is left above the tricuspid valve. (B) Atrial partitioning. Atrial septal defect is enlarged or created. Coronary sinus drains to the pulmonary venous atrium. (LA = *left atrium.)*

A 9-year-old patient with single ventricle {S,L,L}, a narrowed bulboventricular foramen, and previous pulmonary artery banding who underwent creation of a main pulmonary artery–ascending aorta connection along with the Fontan operation required takedown of the Fontan repair on the third postoperative day because of persistent low cardiac output [11].

GROUP 2. One patient (5%) died three days postoperatively. The patient, a 4-year-old child with double-outlet right ventricle, pulmonary stenosis, hypoplastic left ventricle, and a previous subclavian–pulmonary artery shunt, died of persistent low cardiac output and cerebral infarction in spite of postoperative use of a venous assist device [12].

No patient had complete heart block. A 5-year-old child with common atrioventricular canal, pulmonary stenosis, hypoplastic left ventricle, and polysplenia had severe cyanosis postoperatively, which improved after creation of a Glenn shunt on the fourth postoperative day.

Late Results

GROUP 1. There were 3 late deaths (more than 1 month postoperatively). A 2-year-old child with single ventricle and pulmonary stenosis who had the Fontan operation after a simultaneous Glenn shunt and tricuspid valve closure for severe tricuspid insufficiency at 9 months of age died of *Candida*-related sepsis 3.5 months postoperatively. A 13-year-old patient with single ventricle {S,L,L}, pulmonary stenosis, and complete heart block died suddenly at home 3 months postoperatively. The patient had a permanent pacemaker and a Glenn shunt. Postmortem examination revealed major tricuspid patch disruption, which was not necessarily related to the cause of sudden death. A 16-year-old patient with transposition of the great arteries, ventricular septal defect, and hypoplastic right ventricle was managed initially with pulmonary artery banding and a Glenn shunt. At different times, the patient required reclosure of the tricuspid valve and replacement of an occluded right atrium–left pulmonary artery conduit [13]. The patient died 5 years after the Fontan operation of progressive liver failure due to right atrial hypertension from a markedly reduced left pulmonary vascular bed.

In addition to the 2 patients already mentioned who had tricuspid patch disruption, 2 other patients had disruption necessitating reclosure (4/14, 29%).

The 11 long-term survivors have been followed for 2 to 8 years (mean follow-up, 4.9 years). Nine patients are doing well. The patient who required a Fontan takedown is alive 7 years later with a Glenn shunt and a subclavian–pulmonary artery shunt to the left lung. A 15-year-old patient with double-outlet right ventricle and hypoplastic left ventricle, in whom tricuspid patch disruption and heart block developed, has severe myocardial dysfunction 5 years after the Fontan operation.

GROUP 2. There were 2 late deaths. An 8-year-old patient with double-outlet right ventricle, mitral atresia, pulmonary artery banding, and a Glenn shunt sustained conduit occlusion 2 months postoperatively. The Fontan repair was taken down and a shunt established to the left lung. The patient died of sepsis caused by *Candida* 2 months after the last operation. A 13-year-old patient with complete atrioventricular canal, hypoplastic left ventricle, previous pulmonary artery banding, and a Glenn shunt died of renal failure and massive effusion 7 weeks postoperatively. The Glenn shunt was not effective because of the wide-open connection between the superior vena cava and the right atrium.

One patient with common atrioventricular canal, hypoplastic left ventricle, pulmonary stenosis, and polysplenia seen early in this series underwent a Glenn shunt for severe cyanosis in the immediate postoperative period. Patch disruption was discovered 8 years later at cardiac catheterization for progressive cyanosis. The patient is now awaiting closure of the patch disruption.

The 16 long-term survivors have been followed for 4 months to 8 years (mean follow-up, 1.8 years). Fifteen of them are doing well.

Comment

Direct tricuspid valve patch closure either at the annulus or slightly above, with the coronary sinus left to drain into the systemic atrium in the former case and into the systemic ventricle in the latter, has generally been used for patients with two good atrioventricular valves [1, 4, 6, 9, 14, 15], whereas atrial septation has been reserved mainly for patients with a single effective atrioventricular valve [4, 6, 7, 16].

Our experience and that of others with direct tricuspid valve closure at the level of the annulus have been complicated by a high incidence of heart block and patch disruption, especially with continuous suturing [1, 5, 7]. The mechanism of patch disruption is not known, although the combination of superficial bites taken at the area of the conduction system and possible upward pressure on the patch by the tricuspid valve during systole may be contributing factors. The systolic upward pressure on the tricuspid patch in patients undergoing the Fontan operation is greater than that in patients with normal cardiac anatomy undergoing tricuspid valve replacement because it is subjected to systemic pressure and generally has a wider surface area. The incidence of heart block and patch disruption seems lower when the patch is placed above the annulus [5, 6].

Our experience [7] and that of Laks and colleagues [6] with atrial septation in patients with a single effective atrioventricular valve have been encouraging. The extention of use of atrial septation to patients with two atrioventricular valves seems justified [17]. The incidence of heart block and patch disruption is quite low compared with that seen with direct tricuspid closure. Residual atrial defects can be further minimized by intraoperative distention of the left side of the heart. The only patch disruption that occurred in our patients might have been avoided had this maneuver been performed. The theoretical disadvantage of a reduced right atrial volume does not seem to influence the overall results [18]. On the contrary, de Leval and colleagues [19] claim that excluding a dilated atrium from the vena caval blood flow minimizes turbulence and energy dissipation and that exclusion of as much right atrial muscle as possible from the high-pressure circuit may decrease postoperative supraventricular arrhythmias. Humes and associates [20] also reported slightly lower mortality in patients with asplenia or polysplenia undergoing the Fontan operation in whom intraatrial conduits were used.

Early and late mortality rates are comparable in the two groups. Two late deaths that could be attributed to occlusion of the valved conduit probably could have been avoided had a direct atriopulmonary connection been used. With atrial partitioning, there is a theoretical advantage of better myocardial performance, as the coronary sinus is left draining to the lower-pressure left atrium after the Fontan operation [21]. Based on our experience, atrial partitioning is a better approach than direct tricuspid valve closure in the separation of atrial blood flow in patients with complex lesions undergoing the Fontan operation.

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Treatment of Bulboventricular Foramen Stenosis by Ventricle–Ascending Aorta Valved-Conduit Bypass

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An 8-year-old girl with single ventricle and l-transposition developed severe stenosis of the bulboventricular foramen. This became critical subsequent to pulmonary banding and a modified Fontan operation. Successful relief of the obstruction was achieved by placing a valved conduit between the ventricle and ascending aorta, thus bypassing the obstruction.

(Ann Thorac Surg 1989;47:765–6)

Surgical relief of bulboventricular foramen (BVF) stenosis is difficult. We report an alternative technique for bypassing such an obstruction.

The patient, an 8-year-old girl, had a heart murmur and cardiac failure at 7 weeks of age. Cardiac catheterization at that time showed a double-inlet, single ventricle with l-transposition. A subaortic rudimentary outflow tract chamber was connected by way of an unrestrictive BVF to the single ventricle, and an unobstructed pulmonary artery arose directly from the ventricle. Because of intractable cardiac failure, the pulmonary artery was surgically banded when the infant was 3 months of age. She improved progressively, but by 4 years of age, cyanosis appeared.

One year later, repeat catheterization showed the following pressure measurements (mm Hg): main pulmonary artery, 24/14; left atrium (mean), 8; left ventricular end-diastolic, 6.5 to 10.5; BVF gradient, 10. Pulmonary resistance was 1.6 units. A modified Fontan procedure was done when the patient was 6 years old. She improved, but decongestive drugs were still necessary. A new left basilar systolic murmur then became apparent. By 8 years of age, increasing cardiac failure with ascites developed and the murmur was associated with a thrill. Recatheterization showed a gradient of 136 mm Hg across the BVF. Pressure in the ventricle was 212/9 to 14 mm Hg and the pulmonary artery A wave was 22 mm Hg.

At operation, with hypothermia and cardiac arrest, considerable distortion of the pulmonary artery incident to prior banding and Fontan-type procedures was found. A pulmonary artery–ascending aorta bypass procedure seemed technically infeasible. A ventricle–ascending aorta bypass was decided on. The anterior wall of the ventricle was incised at the junction of its middle and distal thirds and a full-thickness elliptical segment of myocardium was excised; the ventriculotomy was enlarged to a diameter of about 25 mm. A Dacron graft 23 mm in diameter with a No. 21 St. Jude mechanical prosthetic valve was sutured into the midportion of the conduit, the proximal end of which was anastomosed, using another running 4-0 Prolene (Ethicon, Inc, Somerville, NJ) suture, to the ascending aorta. Simultaneous aortic and ventricular pressures were equal at the end of the procedure. The patient was weaned from cardiopulmonary bypass without the need for inotropic agents.

When last examined 11 months postoperatively, the patient was doing well, attending school, and gaining weight. Her preoperatively gigantic liver was no longer enlarged, and there was no edema, but decongestive drugs were still necessary to control abdominal swelling.

Comment

In patients such as ours with the common type of single ventricle, stenosis of the BVF is a progressive, often covert, frequent (84%), and potentially lethal problem [1]. The increasing ventricular hypertrophy and fibrosis that BVF obstruction entails elevate ventricular pressures and decrease compliance. Both pulmonary banding and the modified Fontan procedure can initiate or accelerate foramen stenosis [2, 3].

Foramen stenosis has been attacked directly via trans-outlet chamber resection, aortotomy, or right atriotomy, but iatrogenic heart block frequently results. coronary artery and ventricular injury is possible, inadequate resection is frequent, restenosis can occur, and the mortality rate with the direct approach is very high [3–5]. Bypassing the subaortic obstruction by insertion of a ventricular apex–descending thoracic aorta valved conduit has been uniformly unsuccessful [3, 6].

Another approach has been to anastomose the proximal main pulmonary artery, with or without transsection, to the ascending aorta in order to bypass outlet stenosis [2–4, 6, 7]. The distal pulmonary artery is connected either to the right atrium (Fontan) or to the aorta in some fashion (systemic–pulmonary artery shunt). Penkoské and associates [2] reported doing simultaneous arterial switch and modified Fontan procedures to bypass outflow tract obstruction.

It is evident, if only from the variety of operations suggested, that surgical palliation of subaortic outflow tract obstruction in single-ventricle hearts is problematic and difficult. The main pulmonary artery–ascending aorta diversion is apparently the most successful approach to the problem [3]. However, of 19 patients reviewed—all anatomically similar to ours and reported in the English-

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language medical literature since 1981—who underwent this procedure, 8 died: an operative mortality of 42% for the *best* operation to date. Both Rothman and co-workers [3] and Barber and co-workers [4] relate operative success to the magnitude of the subaortic pressure gradient, and found no surgical survivors with gradients greater than 75 and 66 mm Hg, respectively. Only one patient—a surgical nonsurvivor with a gradient of about 140 mm Hg [4]—of all those reported in surgical series since 1981 had a transforamen pressure gradient greater than our patient's 136-mm Hg gradient.

The ventricle–ascending aorta valved-conduit bypass procedure used in our patient has several advantages. It is probably applicable to all ages beyond infancy, and subsequent to pulmonary artery banding and Fontan-type procedures. There is little chance of producing heart block. It is technically easier than dividing and anastomosing the posteriorly located pulmonary artery, especially if it was previously banded. The conduit and valve are replaceable should the need arise because of degenerative changes or patient growth. Valve conduits do, of course, entail the risks of maintenance, and some myocardium is sacrificed when they are placed. An allograft conduit could be used as an alternative to a synthetic prosthesis.

As experience to date with operations for relief of subaortic stenosis in patients with univentricular hearts is so dismal, the ventricle–ascending aorta valved-conduit bypass operation should be considered as an alternative.

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Gastrotracheal Fistula: A Late Complication After Transhiatal Esophagectomy

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A 51-year-old woman underwent a transhiatal esophagectomy for a failed antireflux procedure. She did well for 15 months, when she developed evidence of hemoptysis followed by tracheogastric fistula. She underwent operative repair with the use of a pericardial patch to replace the membranous trachea and interposition of a latissimus dorsi flap to isolate the stomach from the tracheal suture line. She has done well after this operation.

(Ann Thorac Surg 1989;47:767–8)

Transhiatal esophagectomy for resection of tumors of the cervical and thoracic esophagus is a technique that has been in use for approximately 20 years. The technique has been safe and has had few perioperative complications. Membranous tracheal injury has been reported during the procedure, but this usually can be avoided with careful technique [1]. We present a case of late gastrotracheal fistula after transhiatal esophagectomy.

The patient is a 51-year-old woman with a long history of severe esophageal motility disorders. She initially underwent a transabdominal Nissen fundoplication in November 1985 at the time of cholecystectomy at another hospital. Severe dysphagia developed after this, and she underwent motility studies at the University of Virginia, where it was revealed that she had no motility in her esophagus although there was no specific obstruction at the gastroesophageal junction. She underwent takedown of the Nissen fundoplication in January 1986 and had a very loose Belsey mark IV procedure done at that time through a left thoracotomy. Unfortunately she still had dysphagia and also evidence of further gastroesophageal reflux. Finally, due to intractable symptoms, she underwent a transhiatal esophagectomy with gastric pull-up in September 1986. She had a totally benign course after this and had no evidence of any tracheal injury at the time of operation. She was discharged from the hospital 1 week after this operation and has had no difficulty with swallowing. Barium swallow revealed no leaks or obstruction.

She did well for 15 months, then developed mild hemoptysis. She underwent bronchoscopy and esophagoscopy at the end of September 1987 and was noted to have some mild tracheitis at the posterior trachea with no other abnormalities noted. On January 13, 1988, acute respiratory distress developed, and she required intubation at an outside hospital. She was transferred with a respiratory acidosis and stabilized with intubation. Repeat bronchoscopy revealed a large tracheogastric fistula with erosion of half the posterior membranous trachea down to the level of the carina.

The day after admission she was taken to the operating room where she underwent a right thoracotomy. The latissimus muscle was retracted for later use. The stomach was dissected from the trachea and there was noted to be a large communication at the site where the previously stapled suture line along the greater curvature of the stomach had eroded into the membranous trachea. This had been the site where the esophagus had been divided from the stomach. This large opening in the stomach was oversewn with two-layer closure. The tracheal defect was closed with a 4-cm portion of pericardium with a running 3-0 Prolene (Ethicon, Inc, Somerville, NJ) suture. This suture line was checked and noted to be airtight. A pleural flap also was used to cover the pericardial closure on the membranous trachea. The latissimus dorsi flap was interposed between the tracheal and gastric suture lines.

The patient was extubated the day of operation. Her postoperative course was entirely uncomplicated and she was discharged from the hospital ten days after operation. Postoperatively she underwent bronchoscopy, which revealed an intact closure. Barium swallow revealed no evidence of any gastric leak. She has done well at 6 months follow-up without evidence of fistula recurrence.

Comment

Transhiatal esophagectomy avoids thoracotomy in patients with both benign and malignant disease [1, 2]. Membranous tracheal injury has certainly been well described [3]. These injuries occur at the time of operation and usually can be avoided by careful technique. This case report describes a late complication of tracheal erosion by a gastric staple line. To our knowledge, this complication has not been described after transhiatal esophagectomy. We present this case to heighten awareness of the possibility of this complication and to discuss the technique of repair, including a pericardial patch of the membranous

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trachea followed by interposition of a latissimus dorsi flap [4].

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Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hyatt-Regency, Dallas/Fort Worth Airport, Dallas TX, on February 4, 1990. The closing date for registration is August 1, 1989.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Combined Ascending Aorta Rupture and Left Main Bronchus Disruption From Blunt Chest Trauma

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After blunt chest trauma, early diagnosis of associated bronchial, vascular, and esophageal injuries must be attempted, as those lesions may be produced by the same mechanism. We report a case of successful management of associated bronchial transection and injury of the ascending aorta. Aortic repair required cardiopulmonary bypass and the use of prosthetic materials, although gross contamination of the mediastinum from the bronchial disruption is a theoretical contraindication to such a procedure. A separate approach to the vascular and airway injuries allowed successful management of both lesions.

(Ann Thorac Surg 1989;47:769–71)

Tracheobronchial injuries as a result of blunt chest trauma are rare (3% in an autopsy study [1] compared with 18% for injuries of the thoracic aorta and its branches). As far as we know, only 4 cases of successful treatment of a rupture of the ascending aorta have been reported [2–4]. We report what is, to our knowledge, the second case of combined ascending aorta and left main bronchus injury from blunt chest trauma, with special emphasis on the importance of early diagnosis and treatment of such associated lesions.

A 37-year-old man fell from a 5-m-high scaffolding and underwent anterior chest trauma from a heavy weight at the same time. On admission at the local hospital, he had dyspnea and hemoptysis. Evaluation showed an anterior flail chest, subcutaneous emphysema, and a right brachial plexus palsy. He was intubated and transferred to our institution.

Chest roentgenograms revealed a moderate left hemopneumothorax and a wide superior mediastinum. Flexible bronchoscopy showed a complete disruption of the left main bronchus at its origin; selective right intubation was therefore performed. Digital intravenous angiography, completed by aortography (Fig 1), showed partial rupture of the ascending aorta just below the origin of the innominate artery. A Gastrografin (E.R. Squibb & Sons, Princeton, NJ) swallow confirmed integrity of the esophagus.

Surgical intervention was carried out as an emergency procedure in two separate steps. First, median sternotomy was performed after femoral and axillary cannulation. The hemopericardium was evacuated and normothermic cardiopulmonary bypass was started, with perfusion to the coronary arteries maintained by complementary cannulation of the ascending aorta. The ascending aorta was then clamped on both sides of the subadventitial hematoma just below the innominate artery. Division confirmed the rupture of four fifths of the section of the aorta. A No. 34 Cooley prosthesis was inserted between both ends and the sternotomy was closed after termination of the cardiopulmonary bypass.

Second, a right posterolateral thoracotomy was performed. The azygos vein was divided, allowing access to the carina. The disrupted left main bronchus was brought up and intubated through the operating field. An end-to-end anastomosis was performed: the anterior wall was closed with a continuous absorbable suture, and the posterior wall, which is more fragile, with separate absorbable sutures. The anastomosis was protected by interposition of esophagus and mediastinal pleura. The patient was extubated by the end of the intervention.

Postoperative chest roentgenograms showed a secondary right pleural effusion, which resolved after puncture. Recovery was uneventful, and the patient was discharged on the 25th postoperative day after a subsequent bronchoscopy showed no evidence of stricture of the bronchial anastomosis.

Six months later, the patient had totally recovered from his brachial plexus palsy. Results of bronchoscopic and angiographic (Fig 2) control studies were normal. One year after the accident he was in good condition, with normal functional respiratory tests.

Comment

As far as we know, this is the second report of a patient with both transection of the left main bronchus and injury of the ascending aorta after blunt chest trauma [4]. When reviewing the literature regarding associated bronchial and vascular injuries, we found that, although deceleration and high tracheal pressure secondary to closed glottis when trauma occurs are postulated explanations of tracheal injury, a compressive force to the anterior chest existed in the vast majority of cases. The same mechanism has been postulated for injuries to several mediastinal structures: the tracheobronchial tree near the carina, the aortic arch and its branches [5], the superior vena cava

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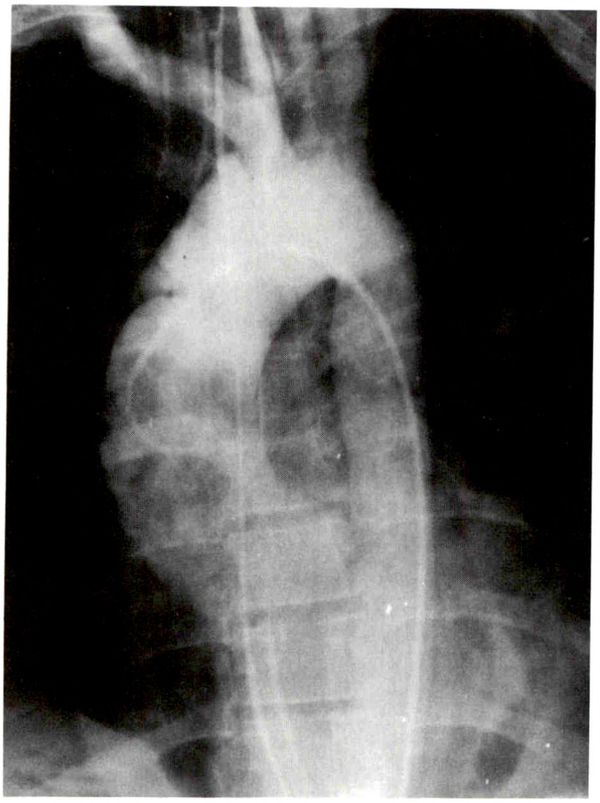

Fig 1. Aortography shows rupture of the ascending aorta just below the origin of the innominate artery.

and azygos vein [6], and the thoracic esophagus (esophagotracheal fistula [7] occurs more often than segmental esophageal injury [8]). Associated lesions, mainly cranial and abdominal, are frequently reported.

Once emergency resuscitation has been performed, further evaluation is required to plan the surgical approach. Digital intravenous angiography is an easy procedure and can be followed by conventional aortography as soon as a vascular injury is suspected. Its indications should be more frequent, according to the possibility of injury to major vascular structures without clinical (pulse asymmetry, supraclavicular bruit or hematoma) or roentgenographic (wide mediastinum, subpleural hematoma, hemothorax) signs. Bronchoscopy should also be performed, considering the fact that approximately 10% of patients with major tracheal or bronchial injuries are asymptomatic. A Gastrografin swallow should be performed as soon as possible to avoid the late diagnosis of esophageal rupture, when mediastinitis is present, or of esophagotracheal fistula, when a cough-swallow syndrome is present.

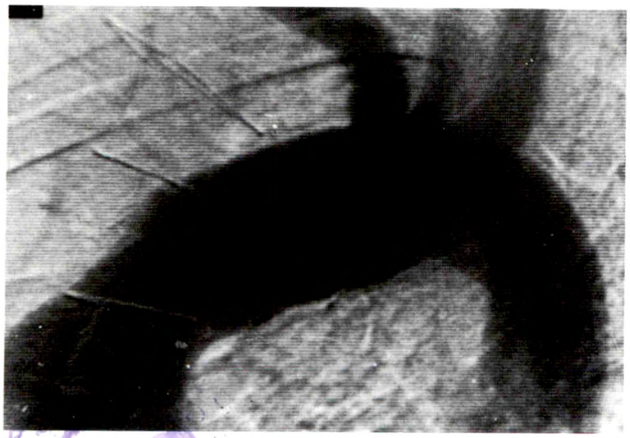

Fig 2. Control angiogram of the aortic bypass graft 6 months after operation.

Selection of patients for such complete evaluation requires analysis of the mechanism of trauma, correlated to clinical and roentgenographic findings. The value of less specific criteria, such as flail chest or first rib fracture, has been discussed; their existence is a hallmark of severe trauma, but usually more specific signs are present that indicate a need for further evaluation. It is less conventional to emphasize that diagnosis of injury to one mediastinal structure calls for search for associated lesions, because the mechanism of injury, rapid deceleration and severe blunt trauma, can produce multiple lesions, as illustrated in our case report. Late diagnosis of arterial injury, although a bronchial injury had been treated early, has been reported. On the other hand, bronchial rupture may be found only at operation, the air leak being masked by the hemomediastinum secondary to a subclavian artery rupture.

Surgical treatment of blunt thoracic vascular injuries may require median sternotomy with possible supraclavicular or cervical extension (to approach the ascending aorta and innominate artery and its branches) or left posterolateral thoracotomy (aortic isthmus and proximal left subclavian artery), whereas more distal subclavian artery injuries are best approached through a combined left anterior thoracotomy and supraclavicular incision. Cardiopulmonary bypass with heparinization may be dangerous in patients with multiple organ injuries, but, unless a small tear allows lateral cross-clamping, it should be considered whenever the ascending aorta is involved, and cannulation performed before starting the sternotomy. Blunt trauma allows graft replacement of the injured vessel if needed, even when associated with a bronchial injury, as long as the diagnosis of the latter allows prompt treatment of both lesions.

Right posterolateral thoracotomy is the best approach to the carina and left main bronchus at its origin. Although an anterior approach to tracheal injuries through a median sternotomy has been described [4, 9], we feel that a separate approach to each lesion, as described in our case report, allows best exposure, best protection of the anastomosis, and best drainage, without a substantial increase in morbidity. Airway management may require cannulation of the distal end of the bronchus, but high-frequency jet ventilation, used in carinal and tracheal operations, should prevent the necessity of ventilation through the operating field.

In conclusion, this case report illustrates the feasibility of managing these two life-threatening injuries, as an emergency procedure, without compromising or delaying either repair.

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REVIEW OF RECENT BOOKS

Cardiac Surgery. Safeguards and Pitfalls in Operative Technique

By Siavosh Khonsari
Rockville, MD, Aspen, 1988
309 pp, illustrated

Reviewed by John W. Hammon, Jr, MD

This text is a new work by a cardiac surgeon, who has published this work as an atlas of techniques in cardiac surgery. He states in the preface that this book is primarily intended for young surgeons in training, although it should appeal to all cardiac surgeons. The text is beautifully illustrated by Joanie Livermore, and these illustrations should receive special commendation. The book itself is a compilation of the experience of Dr Khonsari, pointing up his guidelines for the performance of many of the common procedures in cardiac surgery with highlights on special techniques to make them more interesting and the pitfalls in performing each. The book is extremely basic and most of the techniques standard. There is little new in this text; however, its method of organization and excellent illustrations should make it a valuable reference for surgical training programs and medical school libraries. It would be an excellent purchase for cardiac surgery residents.

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Malignant Fibrous Histiocytoma Associated With a Dacron Vascular Prosthesis

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A case of malignant fibrous histiocytoma associated with a Dacron vascular prosthesis is presented. To our knowledge, only four such tumors have been previously recorded in the English-language literature despite extensive use of vascular prosthetic grafts over the last 30 years.

(Ann Thorac Surg 1989;47:772–4)

It is important that materials used in the construction of prostheses not be associated with risk of malignant change. Although Dacron vascular prostheses have been used extensively, they are normally used in patients with peripheral vascular disease, in whom long-term survival is limited. Current evidence suggests that the risk of malignant change is not increased in the presence of a Dacron vascular prosthesis.

A 57-year-old, male retired electrician was seen at his local medical organization with a 4.5-month history of back pain radiating around the left lower thorax, uncontrolled with nonsteroidal antiinflammatory agents. He was on an invalid pension after a right-sided cerebrovascular accident 5 years previously, from which he had residual minor left arm weakness. He had long-standing atrial fibrillation controlled with digoxin and verapamil. A chest roentgenogram suggested an aneurysm of the lower descending thoracic aorta, and this was confirmed by computed tomography.

Due to increasing pain the patient was admitted to the hospital three days later, and an aortogram demonstrated the saccular aneurysm filling with contrast medium. In view of the possibility of imminent rupture of the aneurysm, surgical repair was undertaken via a left thoracotomy using left heart bypass. There was a 7-cm (diameter) saccular aneurysm of the descending aorta below the hilum of the left lung, to which the lower lobe was partly adherent. At this point the aneurysmal wall was very thin and in danger of rupture. The aorta adjacent to the aneurysm was severely atheromatous and partly calcified. The aorta was clamped above and below the aneurysm, and the aneurysm was opened longitudinally. A moderate amount of old clot was removed and a 20-mm double-velour Dacron interposition graft inserted. The aneurysmal sac was closed around the graft. Recovery was uncomplicated, and the patient was discharged ten days later.

Six months after discharge the patient was readmitted with a 6-week history of malaise, weight loss, and shortness of breath, which had become considerably worse on the day of admission. He denied any pain. He had discontinued verapamil, but was still taking digoxin. Examination revealed a mildly cachectic man in respiratory distress (35 respirations per minute). His atrial fibrillation was uncontrolled (rate, 170/min), with associated pulmonary edema. The white blood cell count was 36,000/μL, and the hemoglobin level was 7.8 g/dL. Chest roentgenogram demonstrated pulmonary edema and a large mass in the left side of the chest.

His left heart failure was controlled with digoxin, verapamil, and diuretics, and his clinical condition improved. However, intermittent fever (37° to 39°C) and leukocytosis persisted. An aortogram demonstrated the integrity of the graft. Computed tomography showed a large mass enveloping the graft and partly compressing the left atrium. Administration of amoxycillin and gentamycin was begun at the time of admission, but apart from fever and leukocytosis there were no signs of sepsis, and serial blood cultures were sterile. Testing the stools for occult blood was negative and there was no evidence to suggest blood loss. The patient received four units of packed red blood cells, with elevation of the hemoglobin level to 12.0 g/dL.

During the week after admission no further change in his condition occurred despite continuing intravenous administration of antibiotics. With a presumptive diagnosis of hemorrhage around an infected graft, removal of the graft was considered necessary. Via a median sternotomy and midline laparotomy a 16-mm Debakey soft woven Dacron graft was anastomosed end-to-side to the ascending aorta and infrarenal aorta (Fig 1). The long anterior incision was closed and the patient repositioned. Via a left thoracotomy the previous Dacron graft was identified in a large mass of pale, firm tumor tissue. The graft was removed, the proximal and distal aortic stumps were closed, and much of the mass was submitted to pathology (Fig 2). Complete removal of the mass was not considered possible.

The cut surface of the tumor nodules showed cystic areas of yellow necrosis in otherwise homogeneous, firm, white tissue. Microscopy revealed a densely cellular, pleomorphic sarcoma with the features of a malignant fibrous histiocytoma. In better differentiated areas plump spindle-shaped cells could be seen forming short, loose fascicles, and a poorly developed storiform pattern was

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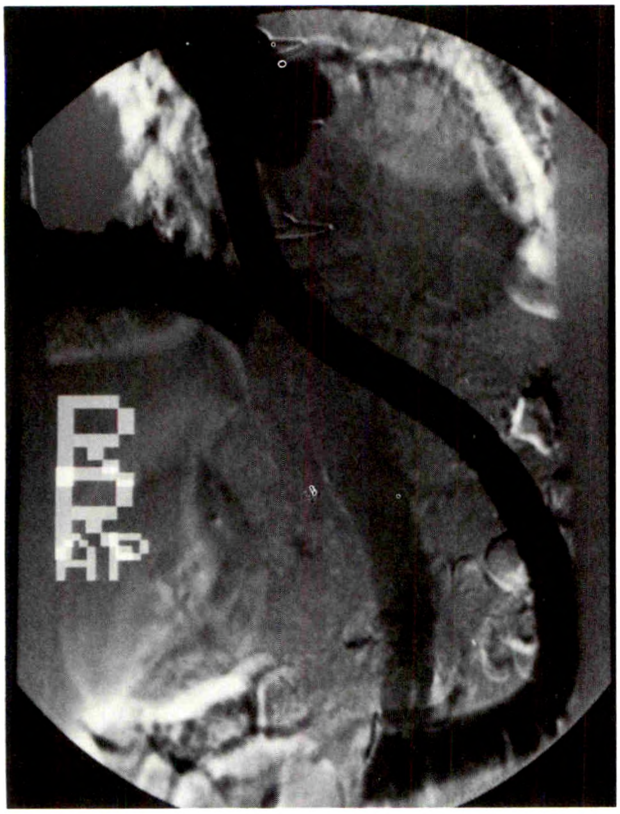

Fig 1. Aortogram demonstrating prosthetic graft from ascending aorta to infrarenal aorta after removal of descending thoracic graft.

evident. Other cellular elements included histiocytoid cells, bizarre multinucleated giant cells, and a reactive inflammatory component. Mitotic activity up to 4 per high power field, nuclear pleomorphism, and hyperchromatism were additional features of this malignancy, no lipoblastic or rhabdomyosarcomatous elements being present. Within the aortic segment, malignant fibrous histiocytoma deeply invaded the elastic wall, but there was no breaching of the sclerotic intima, nor was tumor present within the luminal blood clot.

Postoperative recovery was uncomplicated, the pyrexia abated rapidly, and the patient was discharged 13 days postoperatively. A short course of radiotherapy failed to control tumor growth, and the patient died 10 weeks later. Consent for a postmortem examination could not be obtained.

Comment

Vascular prosthetic grafts of knitted or woven fabrics have been used extensively since Vorhees and colleagues [1] demonstrated their success in dogs in 1951. Improvements in tissue incorporation and reduction in operative blood loss reflect the use of finer filaments of synthetic polymers and improved construction techniques. Polyethylene terephthelate (Dacron) grafts have achieved the greatest popularity since their introduction approximately 35 years ago. Larger numbers of long-term survivors can now be reviewed, and the association with sarcomatous change is seldom seen.

Oppenheimer and associates [2] first demonstrated the association between polymer sheets and sarcomatous change in rats. Subsequent studies with millipore filters showed the importance of pore size in this association [3]. A pore size of less than 0.2 μm is critical to the development of sarcomatous change. The latent period of 1 to 2 years between subcutaneous polymer insertion and sarcomatous change in mice may be extrapolated to several years in humans. Thus, although polymer sheets have proven neoplastic potential in rodents, vascular prostheses composed of polymer fibers are not expected to have a similar potential in humans.

Primary tumors of the aorta are extremely rare. Chen [4] reported a case in 1981 and reviewed the 20 cases previously recorded. To our knowledge, only 4 cases of sarcomatous change associated with a vascular prosthesis have been recorded in the English-language literature [5–8]. All were noted in men living in the United States and were associated with woven Dacron prostheses. The interval between graft insertion and onset of symptoms of sarcomatous change was 4 months, 12 months, 10 years, and 12 years. The interval of less than 6 months in this case confirms the possibility of early neoplastic change.

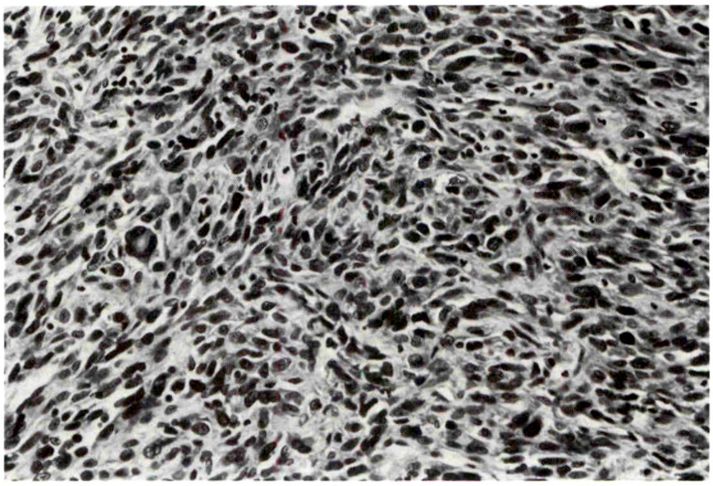

Fig 2. Malignant fibrous histiocytoma showing a cellular, pleomorphic population, including a multinucleated, giant cell form. Scattered mitoses are present, together with a background of benign inflammatory cells. (Hematoxylin and eosin, ×220 before 38% reduction.)

The presentation in this case with pyrexia, anemia, and leukocytosis has been noted in previous case reports of primary aortic tumors. It has also been noted in cases of malignant fibrous histiocytoma in other sites, with a resolution of symptoms after resection. Although the resection here was incomplete, the presenting symptoms largely resolved postoperatively.

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Malignant Fibrous Histiocytoma Obstructing the Thoracic Aorta

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Neoplasms of the aorta are rare. In this report, we present a case of a malignant fibrous histiocytoma that nearly obliterated the lumen of the thoracic aorta. The neoplasm was resected and aortic continuity was reestablished with an interposition graft. This case is particularly unusual because the patient had an isolated lymph node excised 5 years previously that contained the same neoplasm.

(Ann Thorac Surg 1989;47:775–7)

Neoplasms of the aorta are rare. In a recent review, fewer than 25 cases of primary aortic neoplasms were reported [1]. In this report, we present a case of a malignant fibrous histiocytoma that nearly obliterated the lumen of the thoracic aorta.

A 63-year-old, hypertensive woman was admitted to University Hospital with acute midthoracic back pain. Her history included a left axillary node biopsy in 1983 at another institution that showed a malignant fibrous histiocytoma. The neoplasm had been localized to this isolated lymph node and the patient had received no further therapy.

On physical examination, she had a blood pressure of 170/90 mm Hg in the left arm and a pansystolic murmur heard best in the interscapular area. Both femoral pulses were diminished. There was no suspicious adenopathy. Her chest roentgenogram was unremarkable. Contrast-enhanced computed tomography of the chest revealed an irregular filling defect in the thoracic aorta severely compromising the lumen (Fig 1). An angiogram confirmed an irregular narrowing of the thoracic aorta beginning just distal to the left subclavian artery and ending in the midthoracic aorta (Fig 2). There was a 75-mm Hg gradient across the defect. The remainder of the thoracic and abdominal aorta was normal.

At the time of operation, the external appearance of the thoracic aorta was normal and there were no abnormalities in the lungs or mediastinum. A longitudinal aortotomy was made beginning just distal to the left subclavian artery and extending distally for 6 cm. The lumen was found to be nearly obliterated by a "cheesy" material similar to atherosclerotic debris, which was easily evacuated from the aortic wall. There was no evidence of any hematoma, dissection, or aneurysm. A No. 22 low porosity Dacron graft was sewn just below the orifice of the left subclavian artery to a point 2 cm distal to the cheesy material, leaving the posterior aortic wall intact. The pathology of the cheesy material in the aorta revealed a malignant fibrous histiocytoma identical to that found in the previous lymph node biopsy specimen. The tumor had extensive necrosis and was adherent to the surface of an atherosclerotic plaque (Fig 3).

The patient had an uneventful postoperative course until the seventh postoperative day, when she suddenly developed paraplegia. A myelogram revealed a total obstruction at the level of T-9. The patient received 3,000 rads to her lower thoracic vertebrae but her paraplegia persisted. She was discharged home but steady deterioration followed and she died of respiratory complications 6 weeks after operation. A postmortem examination showed no gross tumor at the aortotomy site. There was tumor present in the right iliac crest, the left upper lobe, both adrenal glands, and the ninth thoracic vertebra.

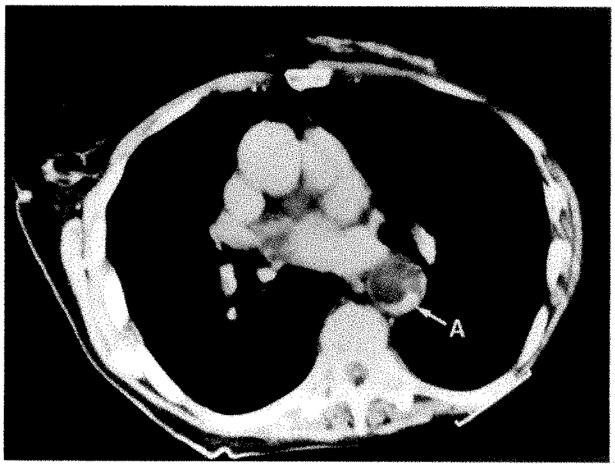

Fig 1. Computed tomographic scan of the thoracic aorta. The aortic lumen (A) is nearly obliterated by a thrombotic mass.

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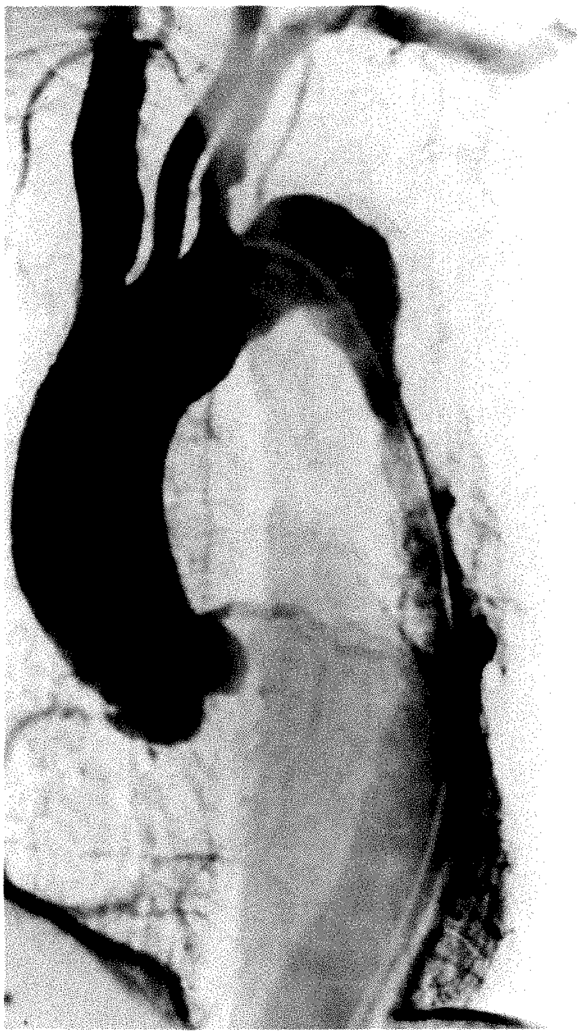

Fig 2. Angiogram of the thoracic aorta. There is an irregular defect of the aortic lumen beginning just distal to the left subclavian artery and extending into the thoracic aorta, but the ascending and distal descending aorta are free of any atheromatous disease.

Comment

Since 1873, there have been fewer than 25 cases of primary aortic neoplasms reported [1]. The most common histological type is a fibrosarcoma, and they can be found in all segments of the aorta except the ascending portion [2–4]. These tumors can assume one of three growth patterns [2]. The polypoid type can form long intraluminal tumor casts with numerous projections into the major arterial branches [5, 6]. The intimal type is characterized by large nodules, which can result in narrowing of the aortic lumen similar to that seen in this patient. The adventitial type, unlike the polypoidal and intimal types, is less likely to produce any luminal obstruction.

The most common presenting symptom is pain, which is usually the result of local tissue destruction or ischemia resulting from obstruction of major arterial branches by embolic or direct tumor involvement [3]. Other symptoms include hypertension, back pain, and claudication. Physical findings may include diminished peripheral pulses as well as a systolic murmur in the interscapular region, as noted in our patient. Computerized axial tomographic scans can confirm the presence of an intraaortic lesion and exclude extraaortic pathology, but they cannot differentiate intraluminal tumor from thrombus. Angiograms will show irregular filling defects projecting into the lumen of the aorta, while the remaining aorta is relatively smooth and of normal caliber. This may help to differentiate tumor from other aortic lesions such as dissection or thrombotic aortic aneurysms [7]. These findings are subtle, and the correct diagnosis was made in less than 50% of all patients reviewed [3].

The prognosis for patients with primary malignant aortic neoplasms is extremely poor. The majority of patients are dead within 3 to 6 months of the onset of symptoms as a result of cachexia, tumor embolism, thrombosis, and widespread metastases [1–3]. The paucity of surgically treated cases makes it difficult to establish principles for managing these neoplasms. Before this report, there have been five reported attempts at surgical treatment for aortic neoplasms [1, 3, 5, 6, 8]. Two long-term survivors with benign lesions were reported by Detrie [6] and Kattus and associates [5]. In patients with malignant neoplasms, primary excisions, endarterectomies, and exclusion techniques have been used with survival not exceeding 1 month [1, 3, 8]. We chose to place an interposition graft to restore aortic continuity, hoping to minimize the threat of tumor embolism and thrombosis. Although surgical intervention is indicated to alleviate pain, relieve the associated hypertension, and prevent tumor emboli, these procedures must be viewed as palliative in view of the extremely poor prognosis associated with these neoplasms.

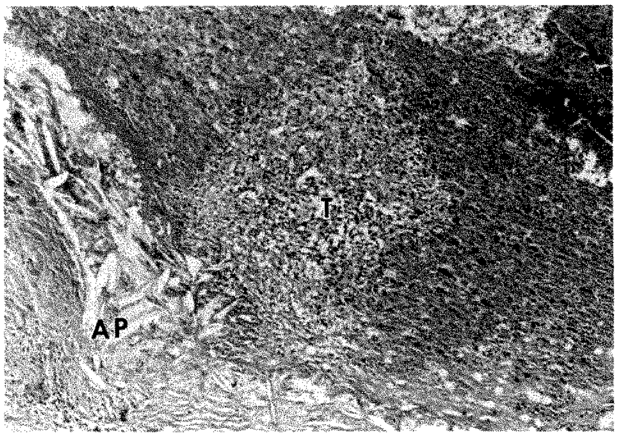

Fig 3. Malignant fibrous histiocytoma. The tumor (T) is adherent to the surface of an atherosclerotic plaque (AP) and grows into the lumen of the aorta, but does not invade the adventitia. (Hematoxylin and eosin, ×40 before 54% reduction.)

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Notice From the American Board of Laser Surgery

The American Board of Laser Surgery announces its fourth Certifying Examination on Saturday, October 14, 1989, at Emory University School of Medicine, Atlanta, Georgia. Candidates may obtain information or application forms from Stanley Stellar, MD, President of the Board, St. Barnabas Medical Center, Livingston, NJ 07039; or Mary M. Cayton, RN, Assistant to the President, 2722 W Oklahoma Ave, Suite 202, Milwaukee, WI 53215.

Traumatic Aorto–Right Atrial Fistula After Blunt Chest Injury

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A extremely rare case of traumatic fistula between the aortic root and the right atrium is reported. The patient was involved in a traffic accident 18 months before admission. Aortogram demonstrated a fistulous tract from the noncoronary sinus into the right atrium. Operation revealed a traumatic dissection of the aortic root with rupture into the right atrium. The aortic dissection was repaired and the patient was discharged from the hospital in good condition.

(Ann Thorac Surg 1989;45:778–9)

Traffic accident is usually the leading cause of thoracic aortic injury [1]. Once aortic injury occurs, less than 1% of the victims have a laceration confined to the intrapericardial sac. Usually, the tear tends to involve whole layers of the aorta, which may cause aortic rupture and immediate death. Occasionally, the tear involves intima and media only, and then progression of the medial hematoma induces a localized aortic dissection, which may also rupture into the pericardium or an intracardiac chamber from the weak point of the adventitia.

This paper reports a rare case of rupture of a traumatic dissecting aneurysm into the right atrium, which is probably the second case in the English-language literature [2].

A 25-year-old, male motorcycle driver struck a tank head on at a speed of approximately 60 km/h in February 1986. He had transient consciousness disturbance immediately. On awakening, only a laceration wound over the skin was noted. The remainder of the physical examination was unremarkable. He was hospitalized uneventfully for three days.

Eighteen months later, he was referred to the National Taiwan University Hospital for evaluation of tightness of the chest. A grade 3/6 continuous murmur was heard over the left sternal border. Chest roentgenogram revealed increased lung markings, cardiomegaly, and no widening of the mediastinum. Electrocardiogram showed bilateral ventricular hypertrophy and left atrial enlargement. Two-dimensional echocardiography and aortography demonstrated an aorto–right atrial fistula [Fig 1]. The hemodynamic data from cardiac catheterization disclosed elevation of the right heart pressure: mean right atrial pressure was 9 mm Hg; right ventricular pressure was 40/13 mm Hg; pulmonary artery pressure was 40/13 mm Hg with a mean of 23 mm Hg; mean pulmonary wedge pressure was 18 mm Hg; and left ventricular end-diastolic pressure was 20 mm Hg. The oxygen saturation in the superior vena cava was 80%, with a step-up to 87% in the lower right atrium. A cardiac catheter could be passed from the aorta into the right atrium.

With a presumed diagnosis of rupture of aneurysm of the noncoronary sinus of Valsalva into the right atrium, the patient underwent elective operation several days later. Intraoperative findings demonstrated a different pathology [Fig 2]. A localized aortic dissection with a transverse intimal tear just above the commissure of the aortic valve was recognized. The false lumen of this aortic dissection communicated with the right atrium via a ruptured hole 3 mm in diameter. The dissection extended from the level of the commissure of the aortic valve up to 4 cm above the commissure circumferentially, and down below the commissure near the aortic annulus. The aortic root and annulus were intact, and the aortic valve was competent. Surgical correction was performed by obliteration of the dissected space and replacement of part of the dissecting aneurysm with a Dacron patch. The patient convalesced steadily in the postoperative period and was discharged ten days after operation.

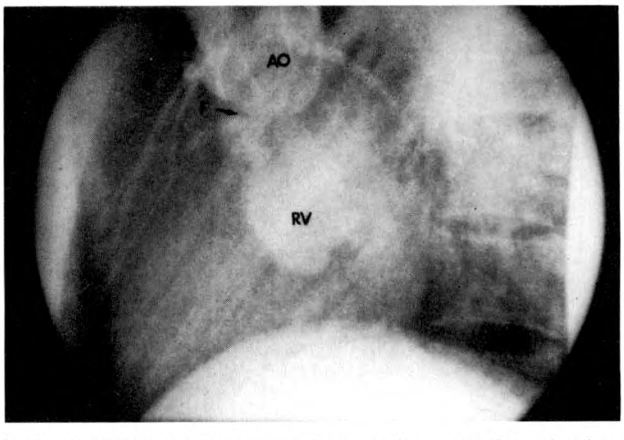

Fig 1. A fistulous tract (arrow) *between aortic root* (AO) *and right atrium with opacification of right ventricle* (RV) *is demonstrated by aortic injection of contrast material.*

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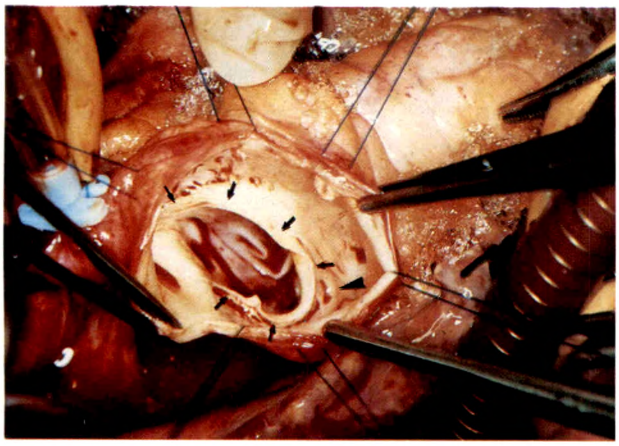

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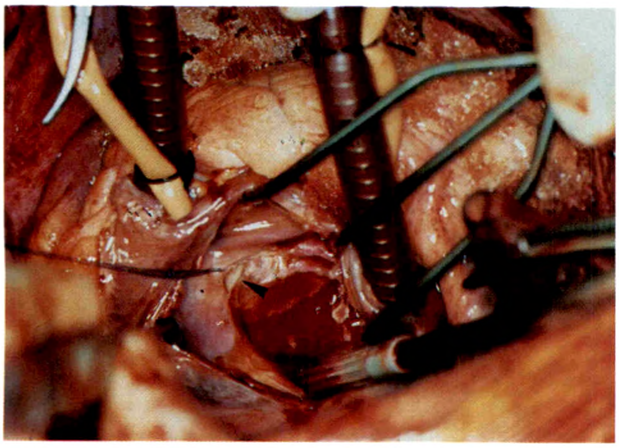

B

*Fig 2. The traumatic aorto–right atrial fistula is illustrated intraoperatively. (A) The traumatic dissection of the aortic root (*small arrows*) and the inlet of the fistulous tract (*large arrowhead*). (B) The outlet of the fistulous tract in the right atrium (*arrowhead*).*

Comment

When traumatic tear occurs at the intima of the aortic root, the dissecting aneurysm develops gradually. The outside layer of the aortic aneurysm behind the sinus of Valsalva may immediately rupture due to a tear of the media in the aortic wall. In the present case, instead of a direct rupture of the dissecting aneurysm into the pericardial cavity, the progression of the medial hematoma dissected the aortic wall into the aortic root where the atrial musculature and atrial endothelium were the only barrier between the aorta and the right atrium. The pressure within the aorta gradually caused this barrier to become thinner. Rupture finally occurred from this weak point due to the high pressure gradient between the aorta and the right atrium.

This patient had blunt chest trauma without other associated injury acknowledged at first. A continuous murmur over the left upper sternal border was heard 18 months after the original accident. The delayed occurrence of aortic rupture is rather rare. The interval between the injury and aortic rupture depends on the pressure gradient and the thickness of preserved septum between the aorta and the neighboring structure. Once aortic rupture into a cardiac chamber occurs, hemodynamic consequence is decided by the amount of blood flowing through the fistulous tract, the rapidity with which the perforation develops, and the chamber that receives the shunt. Due to the delayed aortic rupture, it is hard to differentiate from rupture of congenital aneurysm of the sinus of Valsalva. Examinations may reveal a fistula between the aortic root and the right atrium, but a definite diagnosis can only be confirmed intraoperatively.

A shunt between the aorta and the right atrium shortens the life expectancy to less than 1 year [3]. Therefore, this situation is an absolute indication for surgical correction. Aorto–right atrial shunt may result from some other diseases with cystic medial necrosis such as annuloaortic ectasia and aortic dissection [4]. However, to our knowledge, in the English-language literature the only case of aorto–right atrial fistula secondary to blunt chest trauma that has been previously reported is the one reported by DeSa'Neto and associates in 1979 [2]. The present case is believed to be the second one, and unique in its delayed onset of the fistula.

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Right Mini-thoracotomy: An Adjunct to Left Subcostal Automatic Implantable Cardioverter Defibrillator Implantation

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High defibrillation thresholds are encountered in some patients during implantation of the automatic implantable cardioverter defibrillator (AICD). In a consecutive series of 52 patients with AICD implants, 46 had all-epicardial implants by left subcostal thoracotomy, and 8 of these patients had thresholds greater than 30 J. Placement of an apicolateral large left ventricular patch and an extrapericardial large right atrial patch electrode through a limited right thoracotomy produced substantial reduction in their thresholds. Especially in patients who have had previous intrapericardial operations, this technique provides a simple solution to the problem of high thresholds.

(Ann Thorac Surg 1989;47:780–1)

A number of surgical approaches have been described for implantation of the automatic implantable cardioverter defibrillator (AICD) and its lead system. These include two transvenous leads and an epicardial patch inserted by left thoracotomy [1]; all epicardial lead and patch implantation via left thoracotomy [1]; median sternotomy [2]; subxiphoid thoracotomy [3] and left subcostal thoracotomy [4]; and transvenous and subcutaneous electrodes [5].

Because so many patients who require this device are critically ill, the use of a surgical approach involving minimal dissection and operative time has been desirable. Left thoracotomy has been associated with substantial morbidity. Median sternotomy gives ideal access, but unless other cardiac procedures are to be performed at the same time, this incision is large in relation to the access needed. Subxiphoid thoracotomy provides good access to the right atrium and right ventricle but limited access to the left ventricle. Because of the complications associated with the use of fluoroscopy and transvenous lead insertion in the operating room, and the sizable risk of infection associated with extensive tunneling of transvenous leads down to the abdomen, the all-epicardial approach has been our method of choice.

We first reported the use of the left subcostal approach for epicardial defibrillator patch electrode placement in 1984 [4]. Since then we and others have had extensive experience with this technique. However, occasionally the defibrillation or cardioversion thresholds have been found to be too high despite the trial of a number of combinations of polarity and patch electrode positions through this approach. In these cases, a right anterior mini-thoracotomy has been used to expose the right atrium extrapericardially and place a large patch over it. The purpose of this report is to describe this technique.

Material and Methods

The patient is placed on the operating room table in the supine position and general anesthesia is induced. The entire chest and abdomen are prepared and draped. A left subcostal approach is used to expose the pericardium [1]. The pericardium is opened and the heart is exposed. If extensive adhesions are present, the inferior surface of the heart is dissected from the diaphragm in preparation for intrapericardial electrode placement, but the anterior patch is placed extrapericardially. Sutureless epicardial pacing electrodes are inserted. The defibrillation patch electrodes are placed in position and sutured to the epicardium.

Ventricular fibrillation is induced and defibrillation thresholds are measured. If they are greater than 20 J, the polarity of the patch electrodes is reversed at the connectors. If this is unsuccessful in lowering the threshold to less than 20 J, the patch electrodes are repositioned. The standard electrode configuration has consisted of an anteroapical large patch with its long axis running parallel to the long axis of the left ventricle, midway between the left anterior descending coronary artery and obtuse margin of the heart, and an inferior large patch straddling the septum and overlying the inferior surfaces of the right and left ventricles. Each patch is secured by two 4-0 polypropylene sutures inserted through the shoulders of the electrode. The distal portion of the patches are not sutured. If this configuration does not produce acceptable thresholds even after reversal of polarity the sutures are removed, the anterior patch is moved medially and anteriorly over the right ventricle, and the inferior patch is moved laterally and inferiorly toward the apex and obtuse margin of the heart. If thresholds are still greater than 20 J,

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the anterior patch is removed and placed over the right atrium through the right mini-thoracotomy.

An anterior incision is made at the level of the right atrium, through the bed of the fourth or fifth costal cartilage. The skin incision is extended for about 5 cm laterally from the right sternal border. It is deepened through the subcutaneous tissue and pectoralis major muscle to the surface of the costal cartilage. The perichondrium is incised and elevated and the costal cartilage is excised. The posterior perichondrium and parietal pleura are incised. Care is taken to avoid the right internal mammary vessels in the medial end of the incision. The pleural cavity is entered. The lung is retracted laterally, and the mediastinal pleura overlying the right atrium is exposed. A large patch electrode is placed on the mediastinal pleura against the right atrium near the atrioinferior vena caval junction into the angle between the right atrium, inferior vena cava, and right hemidiaphragm. Thresholds are checked. The patch electrode lead is tunneled to the left subcostal pocket deep to the posterior surface of the sternum. A long hemostat is used to create a tunnel against the posterior surface of the sternum and under the xiphoid process and to draw the lead into the subcostal incision. The AICD generator is connected to the leads. The right lung is fully inflated and the thoracotomy incision is closed in multiple layers, approximating the edges of parietal pleura and perichondrium in the process. No chest tube is used. The left subcostal incision is closed in layers as described previously.

Results

The left subcostal approach for all-epicardial placement of the AICD was used in 46 of 52 consecutive patients receiving AICD implants. In 38 of the 46 patients the epicardial patches could be positioned by the subcostal incision alone, and the threshold achieved was 12.4 ± 6.6 J. In 8 patients, despite multiple attempts at repositioning of patches through the subcostal approach, the thresholds were greater than 30 J. All 8 patients had had intrapericardial operations in the past and the right atrium was inaccessible through the left subcostal incision. A right mini-thoracotomy was performed and a large epicardial patch electrode was placed against the right atrium. Subsequent thresholds were reduced to 20 ± 5.8 J (range, 15 to 30 J). No patient has developed a clinically significant right pleural effusion.

Comment

In view of this favorable experience with the right atrial–left ventricular apical patch configuration we now use this as our initial patch position. The right atrial patch can be inserted through the left subcostal thoracotomy, passed across the anterior right ventricle, and sutured by its shoulders to the edge of the pericardial incision. We have used this approach without mini-thoracotomy in 8 further patients with excellent results. The mean threshold achieved has been 7.4 ± 3.7 J (range, 2 to 10 J).

It has been our goal to obtain a threshold of 20 J or less to ensure an adequate margin of safety, and the validity of this goal has been substantiated by others [6]. Failure to terminate ventricular fibrillation postoperatively has been found to occur when defibrillation thresholds approach the maximum output of the AICD. A margin of more than 10 J has been advocated for successful results with the AICD [6], and we support this conclusion.

In conclusion, we continue to advocate the left subcostal approach for the placement of the all-epicardial system, and in difficult cases we suggest the addition to the procedure of the right mini-thoracotomy.

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Thoracotomy Through the Auscultatory Triangle

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We present a technique of thoracotomy through the auscultatory triangle. Good access to the thoracic cavity is obtained, and both latissimus dorsi and serratus anterior muscles are preserved. There is reduced postoperative morbidity.

(Ann Thorac Surg 1989;47:782–3)

The standard posterolateral thoracotomy incision, with division of the latissimus dorsi and serratus anterior muscles, may cause substantial perioperative morbidity and long-term disability [1–3]. An alternative that we have found quite satisfactory is thoracotomy through the auscultatory triangle, with preservation of both of these muscles. We believe that other thoracic surgeons will find this technique useful.

Technique

Selective endobronchial intubation and single-lung ventilation is used in most cases. The patient is placed in the lateral decubitus position and the usual incision for a posterolateral thoracotomy is made (Fig 1, inset). The key to adequate exposure is full mobilization of the latissimus dorsi and serratus anterior. The superficial surface of the latissimus is dissected from the subcutaneous tissue in a plane just above the muscle fascia with the electrocautery. The auscultatory triangle is identified and the fascia is incised, thus exposing the ribs and intercostal muscles (Fig 1). The posterior border of the latissimus is freed superiorly and inferiorly. A retractor is placed beneath the latissimus and the deep surface of the muscle is dissected. The serratus is likewise mobilized, and the scapula is retracted superiorly (Fig 2).

The pleural cavity is generally entered through the fifth intercostal space with division of the intercostal muscles as far anteriorly and posteriorly as possible. A rib can be resected if further exposure is necessary (Fig 3).

Before closure, an intercostal block is performed with bupivacaine hydrochloride. The ribs are reapproximated with pericostal sutures. When the retractors are removed the muscles return to their usual position. The fascia is closed along the posterior border of the latissimus. The subcutaneous tissue and skin are closed in layers.

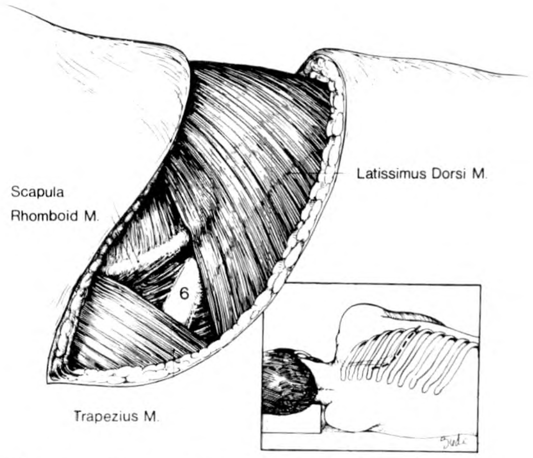

Fig 1. Patient position and placement of the incision are shown (inset). The latissimus dorsi is completely freed. The ribs and intercostal muscles are exposed in the auscultatory triangle.

Comment

The standard posterolateral thoracotomy provides excellent exposure for most operations in the chest; unfortunately, there are some serious drawbacks to this approach. Division of the latissimus dorsi and serratus anterior results in denervation of substantial portions of these muscles. Consequently, there is weakness and restricted mobility of the upper extremity. Also, closure of these muscles is time consuming, and if there is subsequent dehiscence of the wound a large portion of the bony chest wall may be exposed. To avoid these problems,

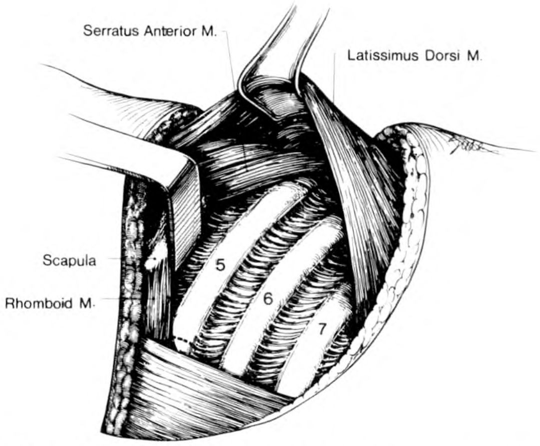

Fig 2. The mobilized latissimus dorsi is retracted anteriorly and the scapula is retracted superiorly.

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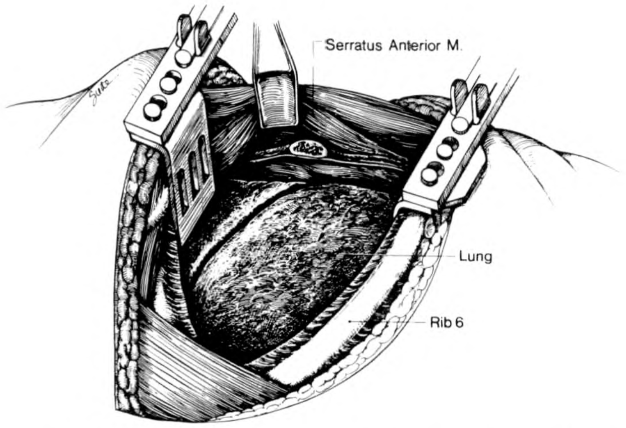

Fig 3. The chest is entered through the fifth intercostal space. Maximal exposure is achieved by resection of a rib.

muscle-sparing thoracotomy has been advocated, and several different methods have been described [1–5].

We present a technique that involves enlargement of the triangle of auscultation by anterior retraction of the latissimus and serratus and superior retraction of the scapula. As no muscles are divided or denervated, shoulder function is recovered rapidly. A paraplegic man who underwent a right lower lobectomy through the auscultatory triangle was able to transfer himself from bed to chair within several days of operation. We feel that whenever possible, muscle-sparing thoracotomy should be used in patients such as paraplegics, amputees, manual laborers, and athletes who are dependent on maximal arm function.

Auscultatory triangle thoracotomy cannot be used in all circumstances. Exposure may be difficult in patients who are obese or heavily muscled, and it may be inadequate for major thoracic vascular procedures. Nazarian and associates [5] state that thoracotomy through the auscultatory triangle is not appropriate in older patients. However, we have successfully used this approach in patients in the sixth decade of life. Exposure can be enhanced by resection of a rib, and if necessary, the incision can be converted to a formal posterolateral thoracotomy by transection of part or all of the latissimus.

In a recent editorial, Kittle [1] asked "Is it not now time for further refinement and consideration of the thoracotomy incision?" We believe that it is time, and that auscultatory triangle warrants serious consideration.

We thank Richard J. Thurer, MD, for reviewing the manuscript. Barbara Siede prepared the illustrations and Lori Mazzone typed the manuscript.

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Extended Use of a Pulmonary Homograft for Right Ventricular Outflow Tract Reconstruction

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When a pulmonary homograft is used for reconstruction of the right ventricular outflow tract a patch or tube extension is usually required to close the gap in the right ventriculotomy. We describe here a simple method by which a large patch can be tailored from the homograft using the distal main pulmonary artery and its branches.

(Ann Thorac Surg 1989;47:784–5)

Recent reports have advocated the use of pulmonary artery homografts for reconstruction of the right ventricular outflow tract (RVOT) because this produces good short-term results [1, 2]. When a pulmonary homograft is used, however, a patch extension is usually required for the proximal anastomosis, to prevent kinking and obstruction as well as to close the gap in the right ventriculotomy. There is no equivalent to the anterior leaflet of the mitral valve, which is present in an aortic homograft.

We describe here a technique by which a large patch can be obtained from the homograft using the distal main pulmonary artery and its branches.

Technique

The proximal end of the pulmonary homograft is properly trimmed and positioned so that a physiological orientation of the valve cusps as described by Kay and associates [1] is obtained. The correct length of the conduit is judged and the distal end cut. The remaining portion including the distal main pulmonary artery and its branches is then incised as shown in Figure 1a to obtain a large patch area (Fig 1b). The distal end of the homograft is then anastomosed to the pulmonary trunk. The proximal end is sutured directly to the superior margin of the right ventriculotomy for about half its circumference. Anastomosing the anterior part of the homograft directly to the right ventricle could flatten the homograft and cause obstruction. The homograft patch is then cut to an approximately semilunar shape; the straight superior edge is anastomosed to the anterior half-circumference of the pulmonary homograft proximally, and the curved inferior edge is anastomosed to the inferior margins of the right ventriculotomy (Fig 2).

Comment

Several solutions have been proposed for patch connection of the proximal end of the homograft valve conduit to the right ventriculotomy [3–5]. Autologous pericardium has been advocated because it does not form peel and because it has been suggested that it may grow with the patient [4]. However, it may not always be possible to obtain a large enough pericardial patch, particularly at reoperation. Synthetic materials, which are readily available, have an inherent tendency toward scar contracture and luminal peel formation [4, 5]. The possibility of obtaining a patch from the redundant part of the pulmonary homograft may obviate these problems, as well as allow the use of one material for the whole reconstruction.

In reporting this simple surgical technique we wish to emphasize the need, when obtaining an homograft, for

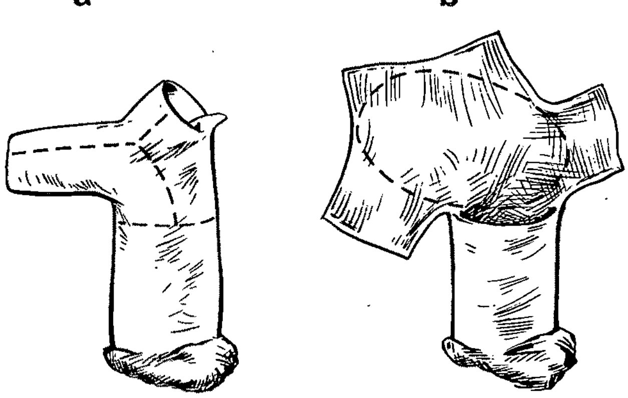

Fig 1. Schematic representation of a pulmonary homograft. (a) The dotted lines represent the lines of incision on the distal pulmonary artery and its branches. (b) The dotted lines represent the area from which the patch can be obtained.

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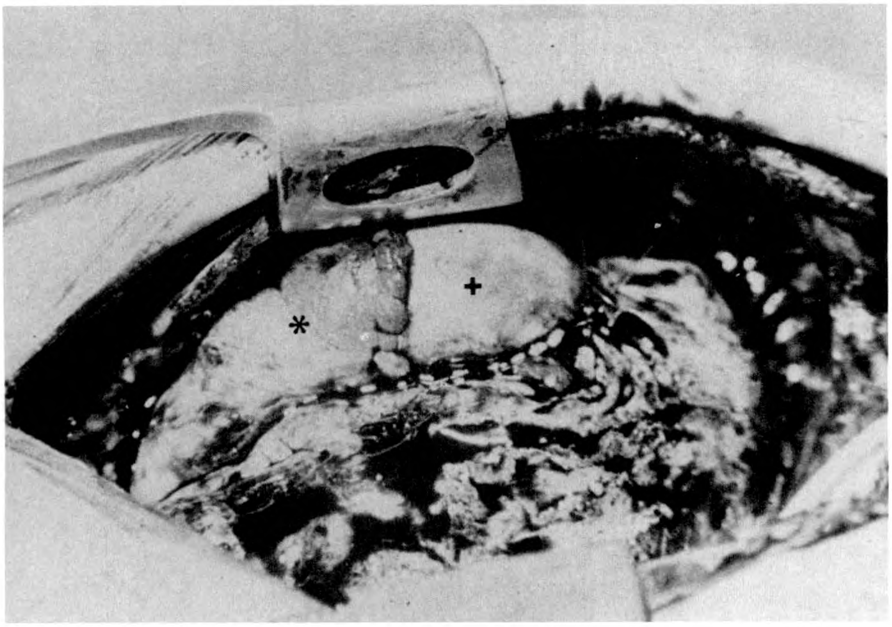

*Fig 2. Completed surgical procedure. * Pulmonary homograft from right ventricle to pulmonary artery. ⁺ Patch extension used to close the gap in the right ventriculotomy.*

transection of the pulmonary arteries at the hilum of the lung to produce as long a donor pulmonary homograft as possible.

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Chemical Pleurodesis in the Presence of Persistent Air Leak

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Persistent air leak makes chemical pleurodesis difficult because the chest tube cannot be clamped after drug instillation. A technique is described that obviates the need for clamping the chest tube in this setting.

(Ann Thorac Surg 1989;47:786–7)

One of the common problems confronting thoracic surgeons is spontaneous pneumothorax. Controversy exists as to the best way of managing this entity. Although most patients with persistent air leaks secondary to spontaneous pneumothorax that does not resolve with tube thoracostomy alone undergo thoracotomy, some are not good surgical candidates, for example, those with poor pulmonary reserve, advanced cancer, or other intercurrent medical problems. In such patients chemical pleurodesis may be effectively used to stop the air leaks. Tetracycline pleurodesis has been widely used for the management of malignant pleural effusion [1, 2]. Clinical and laboratory trials have suggested that it may also be effective for the management of persistent pleural air leaks [3–5]. The standard method of chemical pleurodesis with tetracycline entails clamping the chest tube for a variable period of time after instillation of the drug. In patients with active air leaks, this would result in tension pneumothorax. The absence of tension pneumothorax and progressive subcutaneous emphysema in reported cases suggests that the air leaks were minor and might have resolved without tetracycline. However, for patients with active air leaks of such magnitude that clamping of the chest tube may cause tension pneumothorax, or for those with persistent air leak for more than seven to ten days, we have devised a technique for chemical pleurodesis that requires no clamping of the chest tube, yet allows retention of the instilled agent.

Technique

If the air leak persists beyond seven to ten days after the initial tube thoracostomy and full expansion of the lung, chemical pleurodesis is performed. The tubing connecting the chest tube to the collection bottle is elevated 2 ft (60 cm) above the level of the patient's chest in an inverted U shape and held in place by a string attached to the pole used to support intravenous medications (Fig 1).

The segment of the tubing between the patient's chest and the ascending limb of the inverted U loop can trap a substantial amount of the tetracycline if it is allowed to hang down below the level of the patient's chest. Care should be taken to avoid such an occurrence.

Using sterile technique, 1 g of tetracycline hydrochloride and 250 mg of lidocaine are mixed in 50 mL of 5% dextrose in water, injected into the self-sealing rubber portion of the connecting tube, and allowed to run retrograde into the patient's chest. The chest tube is left off suction and unclamped for six hours. Air can still escape from the chest, but fluid remains inside the pleural cavity and exerts its irritating effect.

The patient is asked to change position in the bed frequently. At the end of six hours, suction is reapplied to the chest bottle and the tubing is lowered. The chest tube is thereafter handled as usual. Additional tetracycline instillation may be carried out in a similar manner if desired. Once the lung remains fully expanded with the chest tube off suction, it is our experience that the air leak soon will stop.

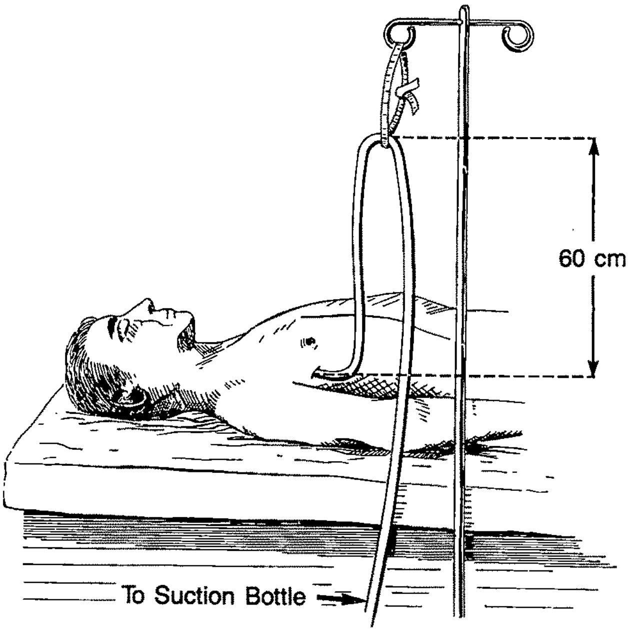

Fig 1. The tubing set up for chemical pleurodesis when persistent air leak is present.

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Comment

In the last 2 years, this technique has been used in 5 patients in the following clinical settings: spontaneous pneumothorax secondary to ipsilateral advanced lung cancer; persistent active air leak after lung needle biopsy in the presence of oxygen-dependent chronic obstructive pulmonary disease; bronchopleural fistula after anaerobic empyema requiring decortication; and spontaneous pneumothorax in two older, debilitated patients with severe chronic obstructive pulmonary disease. All patients except 1 had substantial slowing of the air leak within 48 hours of tetracycline instillation, and in all except 1 the air leak was sealed in three to five days. One patient had recurrence of spontaneous pneumothorax 1 month later and ultimately underwent thoracotomy.

We have used the criterion of at least seven to ten days of persistent air leak before application of this technique, but both shorter and longer times may be appropriate depending on the clinical setting. At present this technique is not being proposed for the good-risk surgical candidates, but rather for those patients in whom great risk or small overall gain would attend thoracotomy.

It is not necessary for the patient to change position in the bed after tetracycline instillation if the lung stays expanded with the chest tube off suction [6].

We think that this simple technique may be useful not only in the settings described above, but in the early management of spontaneous pneumothorax where air leak is present after chest tube insertion.

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Hypothermia: Its Possible Role in Cardiac Surgery

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The current safety of operations on the heart requiring cardiopulmonary bypass occurred because of a series of step-by-step laboratory and clinical investigations that were compromises between the time needed for heart repair and the brain's requirement for oxygen. The first step, so clearly shown in a paper by Bigelow and associates in 1950, was the reduction of the brain's need for oxygen by surface cooling to 28° to 32°C, limited to this level by cardiac and pulmonary failure at levels lower than this. The six to eight minutes of circulatory arrest permitted time for repair of simple defects. This method was rapidly adopted by many surgeons. As low-flow pump oxygenators became available, blood cooling to 10° to 20°C was introduced. This increased the periods of circulatory arrest to 30 to 60 minutes, and also made still longer periods of bypass with the pump oxygenator possible. Hypothermia to reduce oxygen and metabolic requirements is still an important adjunct to bypass, even with the currently used efficient pump oxygenators. It remains the most important component of mycardial preservation, and has made possible the delay needed for transportation between the harvesting and the transplantation of organs.

(Ann Thorac Surg 1989;47:788–91)

Dr Wilfred Bigelow, while serving as a research fellow in 1946 and 1947, made the following observation: "I became aware that surgeons would never be able to correct or cure heart conditions unless they were able to stop the circulation of the blood through the heart, open it, and operate in a bloodless field under direct vision" [1]. His decision to use hypothermia to solve this problem is explained in this quote: "One night I awoke with a simple solution . . . *cool the whole body, reduce oxygen requirements, and interrupt the circulation and open the heart.*"

On Dr Bigelow's return from Johns Hopkins to the University of Toronto and the Banting Research Institute in 1947, he began an orderly investigation in dogs of the physiological effects of surface-induced hypothermia. The report, a landmark in the development of cardiac surgery, was titled "Hypothermia. Its Possible Role in Cardiac Surgery: An Investigation of Factors Governing Survival in Dogs at Low Body Temperatures." This article appeared in the *Annals of Surgery* in 1950 and was coauthored by Drs W. K. Lindsay and W. F. Greenwood [2]. It is a pleasure to read, unencumbered by distracting initials and acronyms, as well as meaningless statistical analyses. This was one of three articles [3, 4] on this subject from Dr Bigelow's laboratory that appeared that year. These findings struck a responsive chord among surgeons everywhere. The great advances of surgery of the thorax in the decade of World War II intensified the sense of urgency to get on with open heart surgery. Intratrachial anesthesia, efficient blood banks, and antibacterial agents made the open chest no longer a major surgical obstacle. The surgeon, using closed heart methods, was building experience with the intraoperative and postoperative management of patients operated on because of heart disease.

What did Dr Bigelow's studies show that created such a great interest? These studies demonstrated that oxygen consumption during surface-induced hypothermia was related in a linear fashion to temperature, providing shivering and fine muscle contractions were controlled by the proper anesthesia. Death from progressive hypothermia in the dog occurred at temperatures around 28°C or slightly colder due to respiratory and cardiac failure. When respiration was controlled by artificial ventilation with 5% carbon dioxide and 95% oxygen, the level of lethal hypothermia could be reduced to 18° to 20°C. Beyond this point, cardiac failure occurred due to standstill or ventricular fibrillation. The heart rate and cardiac output decreased in a linear fashion with the temperature. The venous pressure increased, and if ventricular fibrillation then occurred, sometimes it could be reverted by reducing the venous pressure. The arterial pressure, after a short initial rise, fell slightly and remained stable until the temperature dropped below 24°C, at which it decreased to around 45 mm Hg. Peripheral resistance increased with the temperature reduction. Microscopic observations of the conjunctival vessels showed vascular stasis with cessation of flow in some of the arterioles. The electrocardiogram showed prolongation of both atrial and ventricular conduction times. Periods of heart block were noted, with a regular atrial rhythm sometimes associated with ventricular fibrillation. Potassium and calcium blood levels were observed, but no striking changes were noted. All of these laboratory measurements, in the context of 1988, appear simple. In 1950 they were complex. For example, a blood gas study with Van Slyke apparatus required analyses of two samples of blood and took at least 30 to 45 minutes to complete.

In a paper presented in 1950 before the American Surgical Association [4], Dr Bigelow demonstrated that a period of ten to 12 minutes of circulatory rest was possible at 20°C, permitting time for completion of simple intracardiac procedures. In the course of his report Dr Bigelow mentioned that the lethal hypothermia level of the non-

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hibernating animal was 18° to 20°C, whereas the 3° to 5°C level was tolerated by the hibernating mammal. This was an indication of what Dr Bigelow intended to do in the future and was an expression of his belief that continued studies of hypothermia would lead to a means of more prolonged periods of circulatory arrest [5].

Dr Bigelow's paper had an immediate impact on cardiac surgery. Within a short time Dr F. John Lewis [6] of Minneapolis, and later Dr Henry Swann [7] of Denver, repeated some of Bigelow's experiments and then used this method in the treatment of patients with intracardiac defects. Dr Bigelow was denied the privilege of first applying the procedure he devised in the laboratory to patients because of what he described as a medical atmosphere of reticence regarding heart surgery in his hospital [1]. This is an encumbrance nearly all imaginative cardiac surgeons have borne at one time or other.

Another reason for the enthusiasm for hypothermia was the many problems encountered with pump oxygenators. It appeared that it would be a long time before extracorporeal circulation would become a useful method for open heart surgery. Dr John Gibbon's first studies on the pump oxygenator appeared in 1937 [8], but in 1950 this apparatus was not ready for use on patients. The peculiar response of dogs to extracorporeal circulation was largely to blame. It was then and is still difficult to get survival rates greater than 50% to 60% in normal dogs using a heart-lung machine. It required a great deal of courage to extrapolate these results to patients with sick hearts. Perhaps the success achieved by Warden and associates [9] with cross-circulation removed at least the fear of pumping blood and was important in getting cardiopulmonary bypass from the laboratory to the operating room. The apprehension in using mechanical oxygenators was still present in the 1960s as shown by the proposed use of isolated animal lungs for the oxygenator [1]. The method of Drew and Anderson [10] for open heart surgery eliminated the oxygenator.

The enticing possibility of finding the mechanism for induction, continuation, and reversion of hypothermia in hibernators led Dr Bigelow to greatly expand his studies [1]. These investigations on the groundhog included the construction of a laboratory with underground chambers with observation ports, so that he might observe the animals in the hibernating state. Although at one point in their experiments, Dr Bigelow and his associates believed that they had isolated the chemical that caused hibernation from brown fat, the solution of the interesting problem of hibernation evaded them.

The excitement that followed the paper by Bigelow and associates [2] over the next decade was extraordinary. Hypothermia was recommended for use in many other clinical problems. I once had a research contract with the Air Force [11] that had as one of its goals a possible use of hypothermia for personnel during space exploration. In 1950 there were only 16 references in the *Index Medicus* on the clinical use of hypothermia, mostly for local anesthesia. In 1960, there were nearly 300 references concerned with the use of hypothermia for a variety of clinical problems.

An important milestone for cardiac surgery in 1955 was the first Henry Ford symposium on heart surgery [12]. Nearly all the discussions were on closed heart procedures. Surface hypothermia was discussed as the only method for open heart surgery. In this meeting the use of hypothermia was advocated for the treatment of head injuries and septic shock, as well as for increasing the safe time for occlusion of the vascular supply to the brain for intracranial operations.

Other meetings on hypothermia included a symposium on hypothermia, which was held in 1959 by the New York Academy of Science [13]. In 1960, the National Institutes of Health [14] sponsored a symposium on the clinical use of hypothermia for open heart surgery. In Paris in 1961, an international symposium was held at UNESCO on the use of hypothermia in heart surgery [15]. A special *British Medical Bulletin* in 1961 [16] was devoted to the physiological effects of hypothermia and hibernation and their clinical use.

Methods other than surface cooling for induction of hypothermia for open heart surgery were devised soon after the publication of the paper of Bigelow and associates. Delorme [17], Brock and Ross [18], and Gollan [19] used blood cooling as a method for inducing hypothermia. Mr Drew [20] developed a clinical method of inducing temperatures below 18°C that allowed periods of 60 minutes of circulatory rest. In this unusual technique, the blood was removed from the right atrium, cooled, then passed through the lung by the pulmonary artery. The blood was recovered from the left atrium, cooled further, and then pumped into the arterial system.

In the period of 1956 to at least 1960, most pump oxygenator systems were inefficient and were capable of only oxygenating relatively small amounts of blood per minute. Although Gollan [19] had shown that oxygenators could be safely combined with hypothermia, there was a reluctance of many surgeons to combine these two methods. Dr Dripps [12], in his summary of the NIH Symposium on Hypothermia, made a comment in this regard. My colleagues and I [21, 22] thought that use of these two modalities together was a logical method for carrying out open heart surgery even with the low-flow pump oxygenators then available. In the first step, surface-induced hypothermia was followed by connection to a low-flow pump oxygenator during the time the heart was open. Then a simple heat exchanger was added to the pump oxygenator to rewarm the patient. The last step was not only to warm the patient but to induce hypothermia in this same way. A heat exchanger [23] was developed by Dr Brown with the help of Mr Harold Emmons, an engineer at the Harrison Radiator Company, that was so efficient that it could be used with a low-flow pump oxygenator. Now it was possible to easily induce profound hypothermia of 5° to 18°C. After extensive laboratory studies with this method [24], a patient with tetralogy of Fallot was operated on by Dr Glenn Young using periods of circulatory arrest [25]. She is still alive. This is the first patient on whom profound hypothermia and periods of circulatory rest were used for an open heart operation.

Just as with the use of moderate hypothermia and the pump oxygenator, there was opposition to using deep hypothermia. Although Drew [20], Gordon and coworkers [26], the group at Duke, and several neurosurgeons [27, 28] had shown that this was a safe method, others felt that this degree of cold was likely to damage the central nervous system, and that the damage might be accentuated by other factors such as low perfusion rates and periods of circulatory arrest. Much of this opposition arose from the brain damage reports by Dr Viking Bjork [29]. This attitude existed for nearly 10 years. It was not until the 1970s that the place for deep hypothermia in open heart surgery was established in North America by Mohri and associates [30].

One of the marks of an imaginative and sagacious investigator is the advantage he or she takes of serendipitous events occurring during experimental studies. Dr Bigelow and Dr John Callaghan reasoned that if a respirator would control respiratory failure during hypothermia, the heart's failure resulting from conduction system dysfunction could be controlled with a pacemaker. This might permit lower temperatures and longer periods for open heart operations. A series of studies was then performed using an intracardiac pacemaker to control the heart beat. It turned out that this was not helpful with hypothermia, but this idea was soon applied to treatment of patients with heart block [31].

Who is this surgeon with a message, delivered at the right time, that marked the beginning of a clinical revolution leading to the establishment of cardiac operations among the most commonly done surgical procedures? Dr Wilfred Bigelow is the son of a Canadian surgeon. He was educated in Canada, with his undergraduate medical and surgical training obtained at the University of Toronto and the Toronto General Hospital. After 3 years of training, he served in the armed forces of his country from 1941 to 1946 in a forward surgical unit in the European theatre of operations. In the lull between activities in this assignment, he spent time at Oxford University working with Dr Joseph Trueta, a famous Spanish Civil War surgeon, known for his work on the control of chronic wound infections.

On release from the service, he finished his surgical training and joined the faculty at the University of Toronto. He then received a fellowship in Dr Alfred Blalock's laboratory at Johns Hopkins, where he worked with Dr Richard Bing. On his return to Toronto in 1947, he established a surgical laboratory where many surgeons worked who are now world renowned for their contributions to surgery. Among them were John Callaghan, George Trusler, Griffith Pearson, and Raymond Heimbecker. In the mid-1950s, he organized a thoracic and cardiovascular training program at Toronto. This became one of the most successful training programs in the world.

Dr Bigelow received many honors. Among them were memberships in all the prestigious surgical societies in North America and Great Britain. He served as president of the Canadian Cardiovascular Society, the Society of Vascular Surgeons, and the American Association for Thoracic Surgery.

Where would coronary artery surgery, corrective procedures for complex and acquired intracardiac disorders, intraoperative organ preservation, and organ procurement be without the use of hypothermia? What greater reward or sense of accomplishment can a surgeon have than to formulate an original clinical concept, prove its feasibility in the laboratory, and then see the concept expanded and widely used to benefit a large number of patients in everyday surgical practice?

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Editor's Note

We asked Dr Bigelow for his reflections on the early days of hypothermia.

Dr Bigelow's Commentary

It was not only flattering but interesting to read Will Sealy's perceptive review of the use of hypothermia. He writes with insight and experience.

It must be difficult for the present-day surgeon to imagine an era when hypothermia, related to trauma and surgery, was considered a most dangerous state. The first prerequisite in first aid was warmth. Special heating cabinets on the surgical ward supplied warm blankets, which were wrapped around the patient the moment he or she was lifted from the operating table. Hot water bottles abounded.

The surgeons of the 1940s were right. The shivering that inevitably accompanied a fall in body temperature could drive the oxygen consumption up over 200% which, in a fragile postoperative or posttraumatic state, could cause serious shock. Chemical control of shivering was not known.

Besides the accepted belief that hypothermia increased metabolism, there was another imagined danger. As low body temperature was associated with narcosis, we were advised that hypothermia may damage the brain. Accordingly, to allay this fear, in 1950 with the cooperation of neurophysiologists, the cerebral effects of cooling monkeys was studied under the direction of my dedicated young research fellow by the name of John Callaghan.

There was no evidence of brain damage. As a matter of fact, the intelligence tests indicated a slight improvement after cooling. As a judgement decision, it was decided to disregard this observation as the tests involved food.

Our basic contribution was the demonstration that oxygen consumption fell with body temperature. Our goal, the open heart, was a simple and obvious next step.

The question has been posed—why did we not consummate this research with the first clinical operation? By 1952 we had a zero operative mortality in the laboratory. We were ready. In an adult hospital, the Toronto General, we were vainly looking for a child with a simple lesion as a first case. Bill Mustard at the Children's Hospital was busy clinically with cardiac bypass and a monkey lung as oxygenator.

It was at this time that the enterprising and courageous John Lewis carried out the first clinical open heart operation in history. After 6 years of research, our hypothermia hypothesis had been confirmed.

Actually, our disappointment at not performing the first operation was tempered. As a result of our hibernation research we fully expected to make deep hypothermia and a one- to two-hour open heart available very soon. That would make the eight- to ten-minute operation look quite tame. It was not to be.

Henry Swan's research and surgery extended and popularized the hypothermia technique. At Toronto, in our clinical experience, we benefited from the background of research and the added advantage of residents who had trained in our laboratory. Hypothermia was the most common form of open heart surgery between 1953 and 1959, while the pump technique was undergoing refinements. In some countries this continued for a longer period.

There were two overriding fears in the hypothermia story. One was the original fear of hypothermia just described. The other was the later fear of combining two techniques, hypothermia and the heart-lung pump. Both represented little-understood physiological insults. It was here that Will Sealy and Ivan Brown took the next important step. After careful research they were the first to report clinical success (as early as 1957) in applying the combination of moderate and deep hypothermia with the heart-lung pump. The body temperature was controlled in a novel manner by an efficient heat exchanger.

Deep hypothermia found its most useful function in the surgery of infants. Moderate hypothermia continues to be almost routine in cardiac bypass, and with the advent of cold cardioplegia, hypothermia assumes an interesting role. It has been an absorbing story.

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Mechanical Cardiac Assistance

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REVIEW OF RECENT BOOKS

Computed Tomography of the Chest: A Teaching File

By M. Elon Gale and Joel B. Karlinsky
Chicago: Year Book, 1988
254 pp, illustrated

Reviewed by Linda K. Olson, MD

This book accomplishes the description given in its title as being a "teaching file." The format includes one case per page with a one- or two-paragraph description of the disease entity and the pertinent presenting and/or radiological findings. These paragraphs succintly summarize the radiological features and offer a short differential for each radiographical appearance when appropriate. It is best read from front to back because many of the cases are cross-referenced to other studies in the book. Chapter titles include Normal Anatomy, Pulmonary Parenchyma, Hila and Airways, Mediastinum, Cardiovascular, Pleura, and Diaphragm. All of the common pulmonary entities are demonstrated. In addition, the authors tackle complicated subjects such as the interstitial lung diseases and many multisystem diseases.

The reproductions are outstanding. Only occasional cases are used that were obtained on early scanners and therefore have less detail than one expects with state-of-the-art computed tomographic scanning equipment. Examples of interstitial processes such as UIP, talcosis, and lymphangitic carcinomatosis are presented. Although these entities may be better demonstrated with high-resolution (thin cut, bone algorithm reconstruction) technique, the examples shown are certainly adequate for laying the groundwork for an area of pulmonary imaging that is quite promising.

This book admirably accomplishes its purpose of providing an introduction to chest computed tomography and therefore is most useful to nonradiologists, particularly those dealing with pulmonary diseases and pulmonary surgery.

San Diego, California

CORRESPONDENCE

Stapling of Left Atrial Appendage

To the Editor:

My colleagues and I recently read the article entitled "Ligation of the left atrial appendage using an automatic surgical stapler" by DiSesa and colleagues [1]. I was surprised to see this study, considering that this information has already been published some years ago by our group [2]. In our article we reported the use of the automatic stapling device to close the left atrial appendage in 40 patients undergoing mitral valve operations. This technique has been used routinely since this publication. The duplication of scientific material is readily preventable, considering that every university center has easy access to a computerized literature search. I also question the ethics of killing 14 sheep to demonstrate that the stapling device will close the left atrial appendage, considering that stapling devices have been used for years during pulmonary resections.

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Reply

To the Editor:

Doctor Landymore was kind to bring to our attention his paper published some years ago in the Canadian literature but not referenced in the data base (PaperChase) used in the preparation of our paper. Although routine use has been a justification for the continued practice of many techniques, we felt a careful experimental approach to define the limitations and potential intracardiac complications of staple ligation of the left atrial appendage was justified. The fact that stapling devices have been used for years during pulmonary resections was, in our opinion, irrelevant to consideration of their use on cardiac structures. The ethical issue of killing sheep for this study, furthermore, is moot as all of these animals were also subjects in unrelated investigative protocols.

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High-Frequency Ventilation During Dissection of the Internal Mammary Artery

To the Editor:

Dr Shine and colleagues [1] have proposed the use of high-frequency ventilation during dissection of the internal mammary artery. Their paper was a nicely documented description of a safe technique to minimize interference from the lung while the internal mammary artery is being dissected. Unfortunately, it presents a technique that is probably too complicated for the stated purpose. When the internal mammary artery is to be used, most people agree that the pleural space should be opened widely. With the pleural space widely opened, the lung is very nicely kept out of the way by packing one or two laparotomy pads into the left hemithorax. This keeps the lung completely out of the field.

In our cardiac surgery practice in Harrisburg, PA, my colleagues and I routinely use an oxymetric Swan-Ganz catheter and transcutaneous arterial oxygen monitors. When the left lung is packed away from the internal mammary artery, we observe no clinically significant changes in the arterial or mixed venous oxygen saturations.

Simplicity and cost effectiveness are increasingly important in the practice of cardiac surgery, and I therefore suggest that this less cumbersome technique be considered.

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Repair of Fractured Wire During Sternal Closure

To the Editor:

In the September 1987 issue of *The Annals,* Keogh and Bidstrup [1] presented a simple method for safely repairing a wire broken during sternal closure. In a more recent issue, Brian L. Tell [2] describes another method.

Having broken many wires myself during my training years at McGill University Hospitals under Dr Anthony R. C. Dobell in 1967, I started using a method to repair those fractured wires that I never published due to its simplicity. However, the method used by me was published by Rubio and colleagues [3] ten years after I used it, and ten years before the article by Keogh and Bidstrup.

To quote Mark Twain, "What a good thing Adam had, when he said a good thing he knew nobody had said it before."

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Editor's Note

The Annals of Thoracic Surgery for years has followed the "Ingelfinger Rule," developed by the former editor of the *New England Journal of Medicine,* discouraging authors from asserting claims of priority or "first case." Inevitably, when priority is claimed, it leads to the unearthing of an earlier case or description.

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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery,* 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

General Thoracic Surgery, Toronto, Canada—June 1–2, 1989

For information on this meeting, contact Continuing Education, Faculty of Medicine, Medical Sciences Building, University of Toronto, Toronto, Ontario, M5S 1A8, Canada; or telephone (416) 978-2718.

First International Workshop on Cardiomyoplasty, Paris, France—June 6–8, 1989

This meeting is sponsored by Medtronic. For information on this meeting, contact Convergences, 16 Rue Jean-Jacques Rousseau, F 75001 Paris, France; or telex 216911 F (facsimile, 33-1-40130231).

International Symposium on Surgery for Heart Valve Disease, London, United Kingdom—June 12–16, 1989

This symposium is sponsored by Baxter Edwards CVS Division, Carbomedics, Medtronic, Pergamon Press, Inc, Shiley, St. Jude, and USCI International, and will focus on material and designs of replacement heart valves. The symposium is accredited for up to 30 hours of category 1 of the Physician's Recognition Award of the AMA. For information, contact the Symposium Secretariat, Conference Associates HVD, Congress House, 55 New Cavendish St, London W1M 7RE, United Kingdom; or telephone 01-486-0531 (telex: 934346 CONFAS G; facsimile: 01-935-7559).

International Society for Cardiovascular Surgery/Society of Vascular Surgeons, New York, New York—June 19–21, 1989

For information on this meeeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Western Thoracic Surgical Association, Monterey, California—June 21–25, 1989

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Surgery of the Airways, Boston, Massachusetts—July 17–18, 1989

This course is sponsored by the General Thoracic Surgical Department of the Massachusetts General Hospital and the Harvard Medical School Department of Continuing Education. The course is accredited for 16 hours in category 1 of the Physician's Recognition Award of the AMA. For information contact Harvard Medical School Department of Continuing Education, PO Box 825, Boston, MA 02117; or telephone (617) 732-1525.

Third Annual Meeting of the European Society for Vascular Surgery, Malmö, Sweden—September 3–5, 1989

A satellite symposium on pharmacological intervention to increase patency in arterial reconstructions will be held in the same location on September 6–7, 1989. For information on both symposia, contact the Congress Organisation Bureau, ESVS 89, c/o ICM AB, Geijersgatan 50, S-216 19 Malmö, Sweden.

Nineteenth World Congress of The International Society for Cardiovascular Surgery, Toronto, Ontario, Canada—September 5–9, 1989

For information on this meeting, contact XIX World Congress, ISCVS Administrative Offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Fourth World Congress of the International Society for Diseases of the Esophagus, Chicago, Illinois—September 6–8, 1989

This meeting is sponsored by the American College of Chest Physicians and Smith Kline & French Laboratories and is accredited for hour-to-hour credit in category 1 of the Physician's Recognition Award of the AMA. For information, contact the American College of Chest Physicians, PO Box 93826, Chicago, IL 60673.

The Third Current Controversies & Techniques in Congenital Heart Surgery, Baltimore, Maryland—September 8–9, 1989

For information on this meeting, contact Terry Slade Young, Current Controversies and Techniques in Congenital Heart Surgery, 11 S Paca St, University Square Bldg, Suite 304, Baltimore, MD 21201.

Twenty-fifth Annual Meeting of The Society of Thoracic Surgeons, Baltimore, Maryland—September 10–13, 1989

For information on this meeting, contact George C. Kaiser, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Thirty-eighth Annual Meeting of The Scandanavian Association for Thoracic and Cardiovascular Surgery and The Scandanavian Society for Extracorporeal Technology, Aarhus, Denmark—September 13–16, 1989

For information on this meeting, contact the Secretary of the Congress Committee SATCVS/SCANSECT, Chr. Mouritzen, MD, Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus-Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

Third Annual Meeting of the European Association for Cardio-Thoracic Surgery, Munich, Federal Republic of Germany—October 9–11, 1989

For information on this meeting, contact Organizing Secretariat, Interplan Convention and Visitor Service, Sophienstrasse 1, D-8000 Munich 2, FRG; or telephone 089 59 44 92 (telex: 523183 iplan d; facsimile: 089 59 16 10).

Sixth World Congress of Bronchoesophagology, Tokyo, Japan—October 15–18, 1989

This meeting is sponsored by the Organizing Committee of the Sixth World Congress of Bronchoesophagology, the Japan Broncho-esophagological Society, and the Foundation for Advancement of International Science under the auspices of the International Bronchoesophagological Society. For information, contact the Secretariat of the Sixth World Congress of Bronchoesophagology, c/o Japan Convention Services, Inc, Press Center Bldg, 2-2-1 Uchisaiwaicho, Chiyoda-ku, Tokyo 100, Japan; or telephone 03-508-1213 (telex: J33104; facsimile: 03-508-0820).

American College of Surgeons, Atlanta, Georgia—October 15–20, 1989

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050.

Sixteenth World Congress on Diseases of the Chest and the Fifty-fifth Annual Scientific Assembly, American College of Chest Physicians, Boston, Massachusetts—October 30–November 3, 1989

This meeting is sponsored by the American College of Chest Physicians and the International Academy of Chest Physicians and Surgeons. For information, contact the American College of Chest Physicians, 911 Busse Highway, Park Ridge, IL 60068; or telephone (312) 698-2200.

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association, Phoenix, Arizona—November 9–11, 1989

For information on this meeting, contact Gordon F. Murray, MD, Southern Thoracic Surgical Association, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Sixty-second Scientific Session of the American Heart Association, New Orleans, Louisiana—November 13–16, 1989

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 750-5300.

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 130 Madison Avenue, New York, NY. All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words. There is an additional fee of $13.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad.

SITUATIONS AVAILABLE

Cardiovascular and thoracic surgeon experienced in cardiac surgery as well as general thoracic surgery needed to join the practice of an established thoracic and cardiovascular surgeon in the Los Angeles County/South Bay area. Send curriculum vitae and details of experience.

Please respond to 113, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 113A/E

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to 100, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 100A/G

Cardiothoracic surgeon, BC/BE, recent graduate, to join 3-man group for private practice in 500-bed teaching hospital, Great Lakes area, currently active in cardiac procedures. Practice includes open heart, thoracic, and vascular and pacemaker cases. Replies kept confidential. Send CV, list of cases, and references.

Please respond to 101, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 101A/F

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae, photograph, and names of references.

Please respond to 102, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 102B/I

Faculty position: The Division of Thoracic and Cardiovascular Surgery, Southwestern Medical School of the University of Texas Southwestern Medical Center, is seeking an individual with strong clinical background in adult cardiovascular/thoracic surgery, along with a commitment to education and research, for a position at the assistant professor level. Must be ABTS certified or eligible.

Send complete curriculum vitae to W. Steves Ring, MD, Chairman, Division of Thoracic and Cardiovascular Surgery, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9031. An equal opportunity employer. 121B/G

Cardiovascular and thoracic surgeon: BE/BC wanted to join progressive, established cardiovascular/thoracic surgeon in a 72-doctor multispecialty group in a Big-10 University community of 100,000 with superb cultural advantages. Initial guarantee and fringes with early associateship. Subsequent income based on productivity.

For confidential consideration, please submit curriculum vitae to 103, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 103B/H

Cardiothoracic surgeon needed to join established southern California practice. Superb salary, benefits, and lifestyle. Please send curriculum vitae.

Please respond to 108, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 108C/E

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland, OR 97213-2282. 124C/I

Thoracic-vascular surgeon: Board certified or eligible surgeon wanted to join very active noncardiac thoracic vascular practice in small community with referral base of approximately 125,000. Salary leading to full partnership. Advantages of living in a small community in eastern Ohio less than one hour from large desirable metropolitan area. Will also consider applicants primarily interested in vascular surgery. Respond with curriculum vitae.

Please respond to 107, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 107C/F

Cardiovascular and thoracic surgeon BC/BE wanted for established 3-man group in Northeastern Ohio. Adult cardiac, vascular, and thoracic experience needed. Please send curriculum vitae.

Please respond to 106, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 106C/E

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV and photo.

Please respond to 105, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 105C/H

Postresidency clinical associate position available in cardiopulmonary surgery with University-based large service starting July 1989 or January 1990 for 1 to 2 years. Up to 25% research opportunity option available. Complete training in cardiopulmonary surgery desirable. Must be a graduate of an American medical school and eligible for full licensure in Oregon.

Please respond to Albert Starr, MD, 9155 SW Barnes Rd, Suite 240, Portland, OR 97225. 122C/E

Cardiothoracic surgeon to join established group in northwest Indiana (very near Chicago). Excellent salary. Please respond with curriculum vitae.

Please respond to 104, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 104C/H

Cardiovascular and thoracic surgeon wanted for an established practice in Dallas, TX. Candidate must be board certified or eligible.

Please send curriculum vitae to Dallas Cardiovascular Surgery Associates, 7777 Forest Lane, Suite A-323, Dallas, TX 75230. 123C/E

First Assistant, Cardiovascular Surgery: Excellent opportunity to join a dynamic 200-physician multispecialty clinic; located in northeastern Pennsylvania, in a challenging position as a Physician's Assistant. Outstanding noncontributory benefits and competitive salary.

Please send resume to Guthrie Clinic, Guthrie Square, Sayre, PA 18840; or telephone (717) 888-5858. 126D/F

Excellent professional opportunity for cardiothoracic surgeon to join director of new adult cardiac and thoracic surgery program in California wine country. Beautiful semirural geographical surroundings, easy access to San Francisco, desirable area for family. Send curriculum vitae, photo, references—new graduate preferred.

Please respond to 110, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 110D/F

Cardiothoracic surgeon: BE/BC, wanted to join established 3-man practice in southern California. Very busy team doing 1,000 cases/yr. Excellent location and benefits. Practice includes all aspects of adult cardiac, thoracic, and vascular surgery. Please respond with curriculum vitae and recent photograph.

Please respond to 111, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 111D/F

Thoracic surgeon/thoracic oncology: Full-time staff position available for highly qualified, board certified individual at major teaching institution in New York City.

Please respond to 109, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 109D/E

Cardiothoracic surgeon wanted for busy, expanding Southeastern private group in regional medical center with university affiliation. Practice includes most aspects of adult and pediatric cardiac and thoracic surgery. Surgeon must be board eligible or certified with contemporary training. Excellent opportunity for suitable applicant.

Please respond to 112, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 112D/G

Thoracic and vascular surgeon, board certified or board eligible, for very active noncardiac thoracic-vascular practice. Private group in northern New Jersey. Full partnership after acceptable period.

Please respond with curriculum vitae to 145, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 145E

The Division of Cardiothoracic Surgery at the Albany Medical College is seeking two academic cardiac surgeons with excellent clinical skills and proven records of accomplishment in clinical and laboratory research demonstrated by publications and extramural grant awards. The successful candidate must be certified by the American Board of Thoracic Surgery and qualify for a faculty appointment in the Department of Surgery of the Albany Medical College. The Division offers a stimulating professional environment including an approved cardiothoracic residency, an active research laboratory, a well-developed practice of cardiac and thoracic surgery, and a competitive salary and benefit package. Albany Medical College is an affirmative action, equal opportunity employer.

Please send curriculum vitae and three letters of recommendation to: Martin F. McKneally, MD, Division of Cardiothoracic Surgery, Albany Medical College, A-61, ME 702, Albany, NY 12208. 134E

Cardiovascular and thoracic surgeon, BC/BE, needed to join busy expanding private practice in the midwest. Excellent program, large number of experienced cardiologists. Initial contact should include curriculum vitae and references.

Please respond to 141, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 141E

Cardiovascular/thoracic surgeon for expanding 2-man practice in northwest Florida. Primarily adult cardiac surgery, doing 350–400 cases per year. Please respond with curriculum vitae and references.

Please respond to 137, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 137E/G

Physicians—Deborah Heart & Lung Center is currently seeking qualified physicians for fellowship training or surgical rotations in adult and pediatric cardiovascular thoracic surgery. Outstanding educational opportunities with excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Dept of Thoracic & Cardiovascular Surgery, Deborah Heart & Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; or telephone (609) 893-6611, Ext 353. 139E

Cardiothoracic surgeon: Full-time board certified or eligible surgeon wanted for 1,200-bed New England VA Medical Center with excellent academic affiliation and active research program.

Please contact Shukri F. Khuri, MD, Chief of Surgery, West Roxbury VA Medical Center, 1400 VFW Pkwy, West Roxbury, MA 02132. An equal opportunity employer. 140E

Board certified or eligible thoracic and cardiovascular surgeon in large metropolitan area in the Midwest. Immediate opening. Adult cardiac, peripheral vascular, and thoracic surgery. Apply with curriculum vitae, three references, and recent photograph.

Please respond to 142, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 142E

Cardiothoracic surgeon, BE/BC, to join established 2-man private practice involved with adult cardiac, thoracic, and vascular surgery in major Midwest community. Minimum 3 years experience. Salary leading to partnership. Please send CV, photo, clinical experience, and references.

Please respond to 143, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 143E/G

Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits.

Please respond with curriculum vitae to 144, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 144E/D

Cardiothoracic surgeon needed to join established 2-man group in practice of adult cardiac, pulmonary, and vascular surgery. Must be board certified or eligible and graduate from a US medical school.

Please respond to R. W. Ruess, MD, 1834 Broadway, Cape Girardeau, MO 63701. 149E/G

Thoracic-vascular surgeon: Excellent opportunity for a board-certified or board-eligible noncardiac thoracic-vascular surgeon to join group practice on south shore of Long Island. Associated with two large level II 400-bed hospitals, fine recreational facilities, including beaches and boating, quality schools, and excellent homes.

Please respond to 148, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 148EGIKA

Consultant cardiothoracic surgeon to the Department of Cardiothoracic Surgery, The National Hospital, University of Copenhagen: The department is a 48-bed unit with open heart as well as classic thoracic surgery. The main area of work for the applicant will be coronary artery surgery, but the applicant must be experienced in all areas of heart surgery as well as classic thoracic surgery, and must demonstrate an interest in research work. Application (9 copies) containing curriculum vitae should be addressed to Her Majesty, the Queen. The applications and 5 copies of scientific works must be received no later than April 30, 1989.

Please respond to Direktionen for Rigshospitalet, Blegdamsvej 9, 2100 Kobenhaven O., Denmark. 147E

Cardiothoracic surgeon/BC/BE: to establish a cardiothoracic surgery practice in 29-doctor multispecialty group practice. Local 579-bed hospital has received C.O.N. for cardiac surgery. Competitive salary and incentive plus benefit package. Located in Central Florida, lake country.

Please respond to 150, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York. NY 10010. 150E/G

SITUATIONS WANTED

Cardiovascular and thoracic surgeon, 42, American, ABS, ABTS, ABVS. Eight years private practice experience. Completing overseas fellowship in heart and heart/lung transplantation July 1989. Seeks opportunity with program involved in transplant surgery. Curriculum vitae and references upon request.

Please respond to 119, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 119A/E

Cardiovascular and thoracic surgeon, 40, wishes to relocate, preferably in the Southeast. American university trained, ABS, ABTS, FACS. Private practice experience in adult cardiac, thoracic, and peripheral vascular surgery. Willing to initiate new program. Curriculum vitae and references upon request.

Please respond to 114, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 114A/F

Chief resident in cardiothoracic surgery in major New York training program, finishing June 1989. Interested in private practice in Northeast. Curriculum vitae and references upon request.

Please respond to 115, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 115B/E

Cardiovascular and thoracic surgeon wishes to relocate. University trained with ABTS certification. Ten years' experience with extensive cardiac, thoracic, and peripheral vascular surgery. Would be interested in starting new program or association with group. Curriculum vitae and references available upon request.

Please respond to 117, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 117C/H

Pediatric and adult cardiovascular surgeon, 33, board eligible, seeking staff position. Extensive training in both complex congenital and adult valve and coronary surgery. Experienced in internal mammary artery grafting. Proficient in preoperative and postoperative management of adult and pediatric patients. Curriculum vitae and references on request.

Please respond to 116, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 116C/F

General thoracic surgeon, 38, trained abroad and US, qualified as general and thoracic surgeon (foreign boards), FMGEMS, FLEX, wishes to relocate to an English-speaking country. Extensive training and experience in thoracic oncology, trauma, infections, and reconstructive surgery. Curriculum vitae and references available on request.

Please respond to 118, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 118D/E

Cardiovascular and thoracic surgeon, 37, ABS, ABTS, personable, strong technical skills and patient care, interested in joining group or starting new program.

Please respond to 133, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 133E/H

Cardiothoracic surgeon, 38, ABS, ABTS, university trained with academic practice experience. Additional fellowship training with transplant and homograft experience. Also experienced in internal mammary artery grafting, redo operations, valve and coronary artery cases, as well as extensive thoracic and pulmonary experience. Curriculum vitae and references available on request.

Please respond to 135, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 135E

Cardiovascular and thoracic surgeon wishes to relocate. ABS, ABTS with 10 years experience in adult cardiac, thoracic, and peripheral vascular surgery. All areas considered. Willing to initiate or help initiate new program.

Please respond to 136, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 136E/H

Cardiovascular and thoracic surgeon, extensive experience, ABS, ABTS, university trained. CABG with IMA and vein, mitral valve reconstruction and valve replacement, extensive pulmonary and vascular experience including laser angioplasty. Solid research interest with 90 published papers. Wishes to join active cardiothoracic practice. Curriculum vitae and references on request.

Please respond to 138, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 138E/G

FELLOWSHIPS

Fellowship in thoracic and cardiovascular surgery available July 1989.

Contact Dr Harold C. Urschel, 3600 Gaston Avenue, Suite 1201, Dallas, TX 75246; telephone (214) 824-2503. 129A/F

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819. 130A/F

Surgical fellow: Clinical fellowship position available in adult and pediatric cardiothoracic surgery. Large volume of cases. NJ license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Dept of Surgery, Deborah Heart & Lung Center, Browns Mills, NJ 08015. 132A/E

Clinical fellowship in adult cardiothoracic surgery available. Excellent stipend and fringe benefits.

Please send curriculum vitae to Eldred D. Mundth, MD, Bryn Mawr Medical Building, North, 830 Old Lancaster Road, Bryn Mawr, PA 19010. 131A/E

Cardiac surgery research fellowship: Research fellowship in cardiac surgery available for 1–2 years beginning in July 1989. Major projects include laboratory and clinical research in cardiomyoplasty, the use of skeletal muscle for cardiac assist. Position also provides access to leading thoracic surgery training program. Salary is negotiable.

Contact James D. Sink, MD, The Emory Clinic, Section of Cardio-thoracic Surgery, 1365 Clifton Road, NE, Atlanta, GA 30333; (404) 321-0111, Extension 3616. 120B/E

Senior Fellow in Thoracic and Cardiovascular Surgery at the Lahey Clinic Medical Center, Burlington, MA, available from July 1, 1990, to December 31, 1990. This position will involve all aspects of cardiothoracic surgery, with special emphasis on pulmonary and esophageal surgery. Opportunity for clinical research.

Address inquiries to David M. Shahian, MD, Chairman, Department of Thoracic and Cardiovascular Surgery, Lahey Clinic Medical Center, 41 Mall Rd, Burlington, MA 01805. 127C/E

Fellowship in adult cardiac surgery available July 1 for 1 or 2 years in private program performing over 600 open heart procedures yearly. Full general surgery training required. ECFMG and visa-qualified foreign applicants accepted.

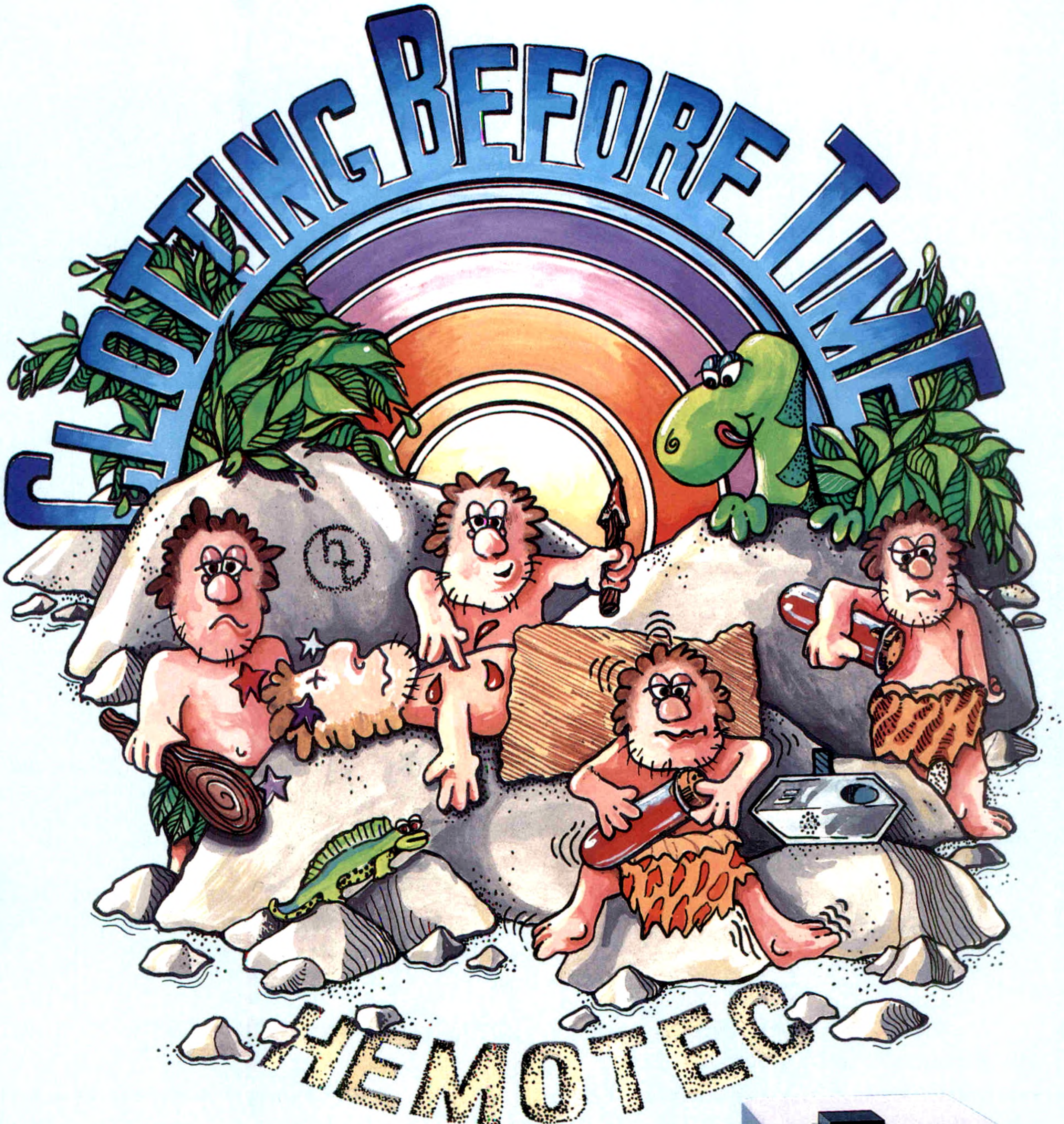
Send curriculum vitae to Donald R. Kahn, MD, 817 Princeton Ave, Suite 300, Birmingham, AL 35211. 125C/E

Fellowship in thoracic and cardiovascular surgery available July 1, 1989. Good salary and all expenses paid. Research opportunities.

Please send inquiries to George C. Morris, Jr, MD, and Gerald M. Lawrie, MD, Baylor College of Medicine, Houston, TX 77030; or telephone (713) 797-9428. 128D/F

Research fellowship in cardiovascular surgery including wide range of research topics is available for 6 to 12 months in the Cardiac Surgery Research Center of the Hadassah University Hospital in Jerusalem.

Please contact Prof Gideon Uretzky, Joseph Lunenfeld Cardiac Surgery Research Center, Hadassah University Hospital, POB 12000, Jerusalem 91120, Israel; or telephone 446790. 127D/F



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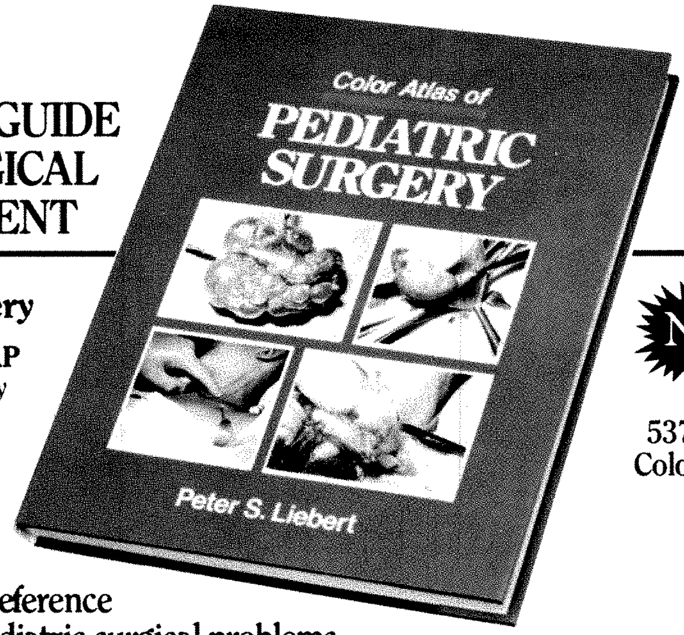

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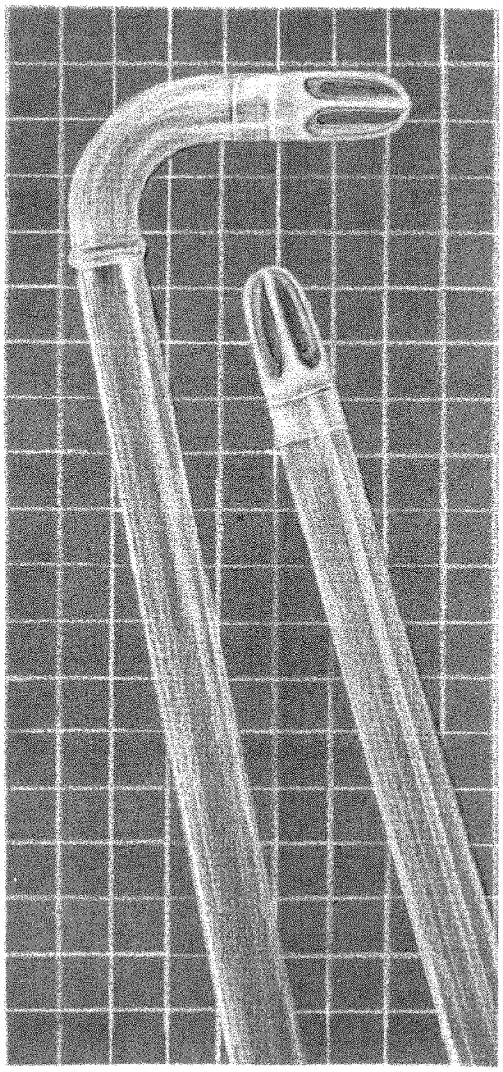

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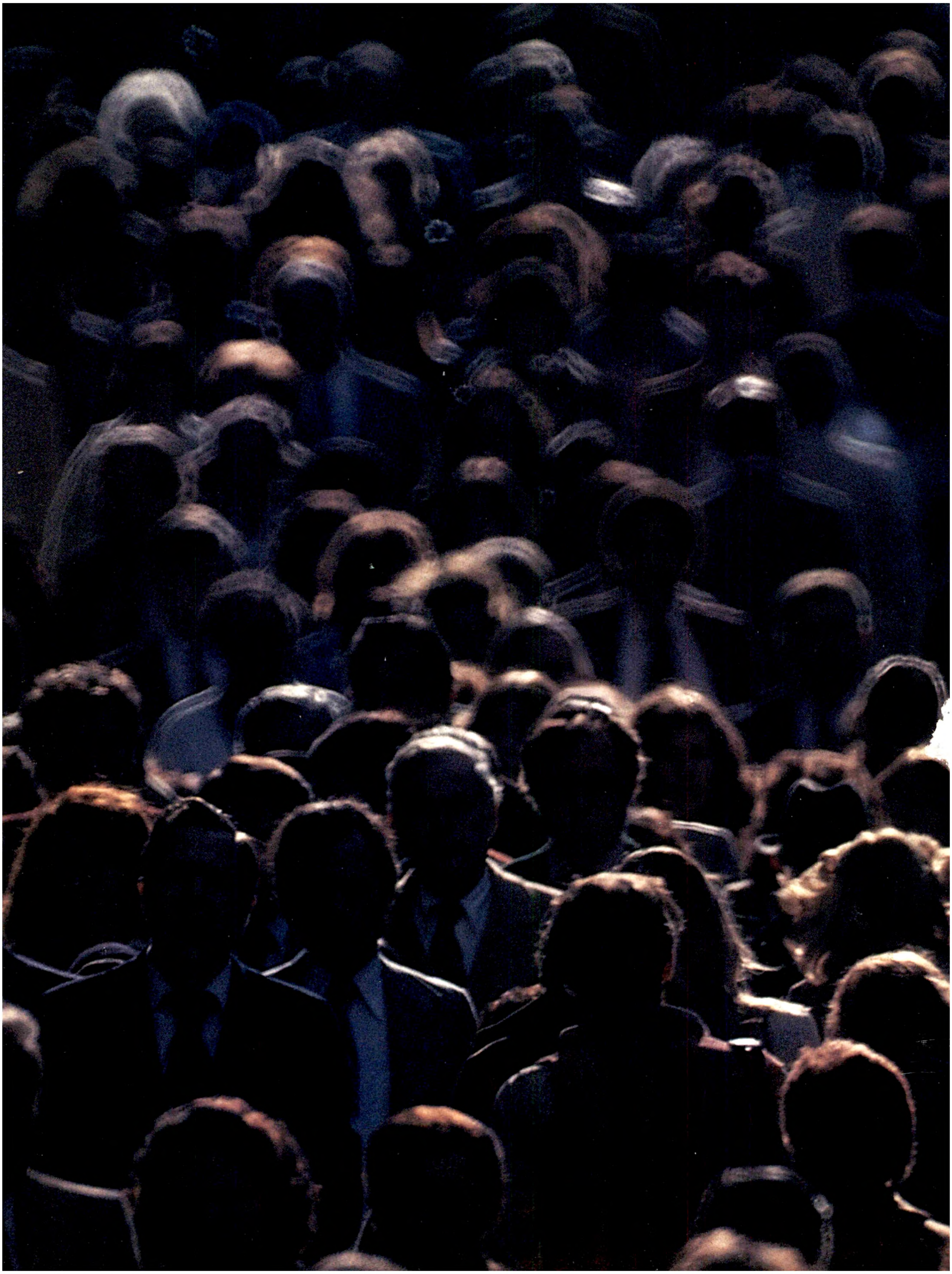

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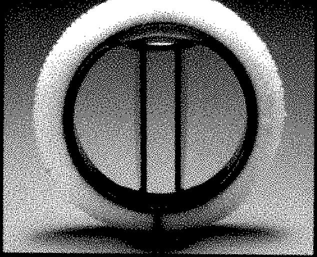

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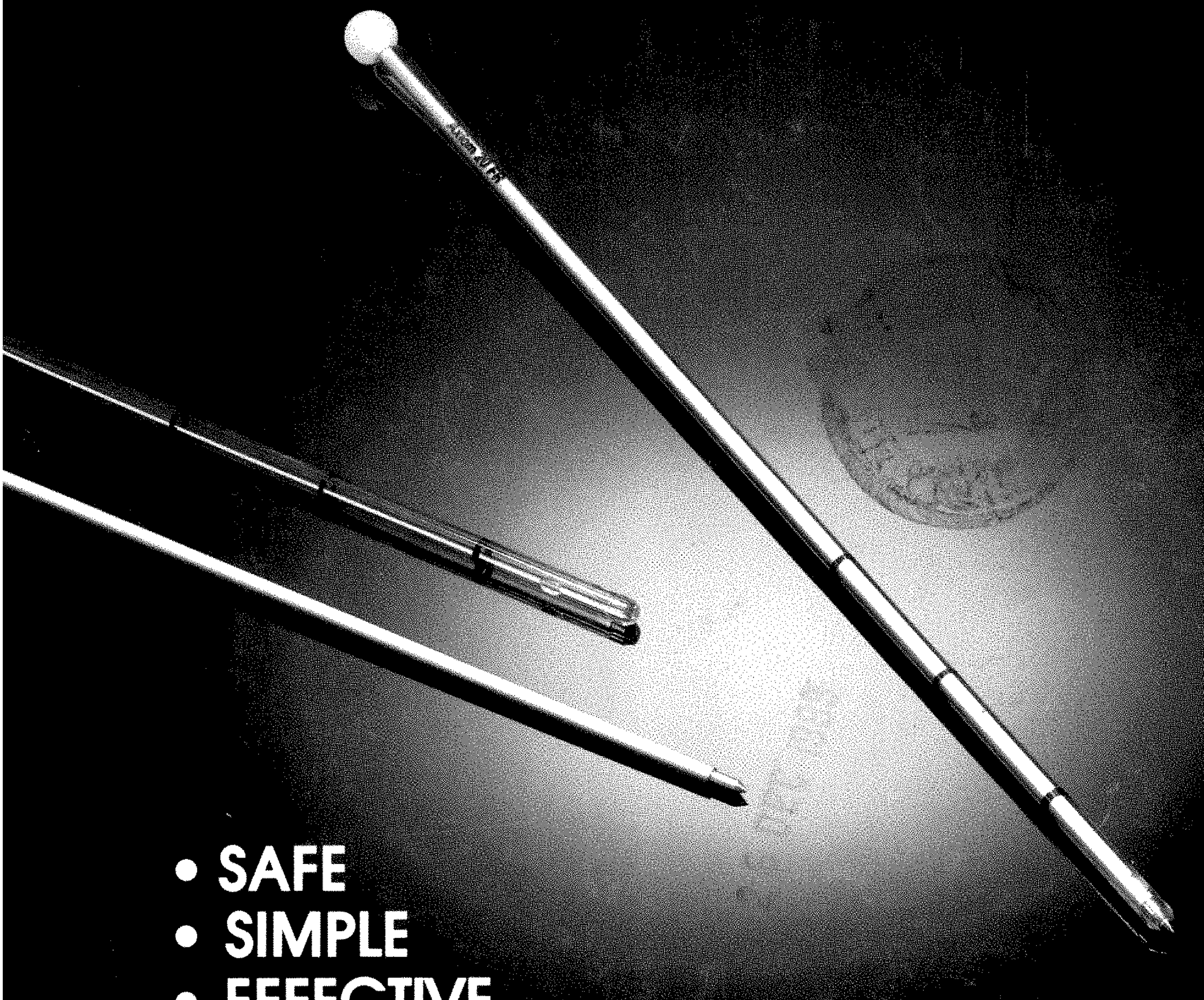

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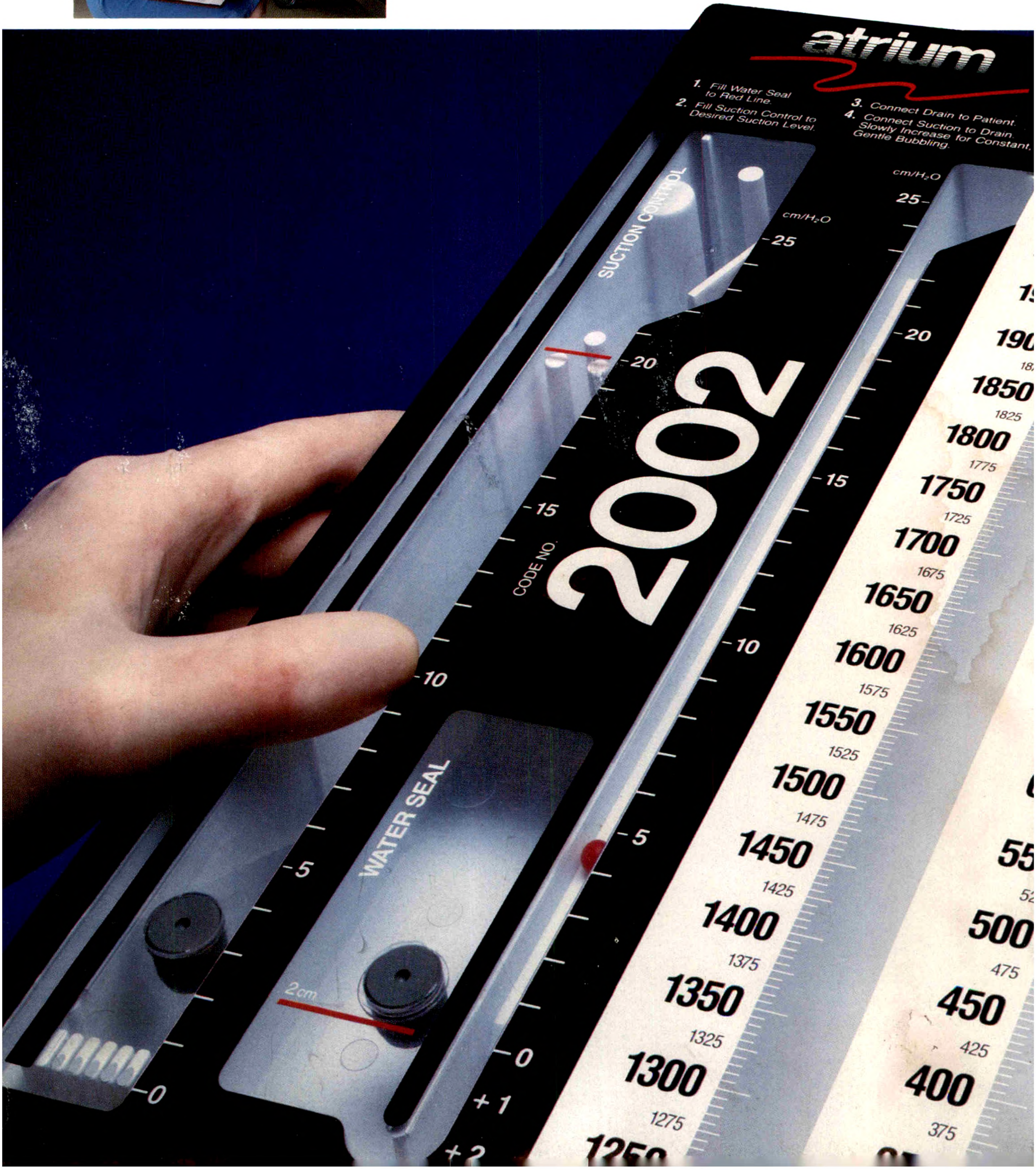
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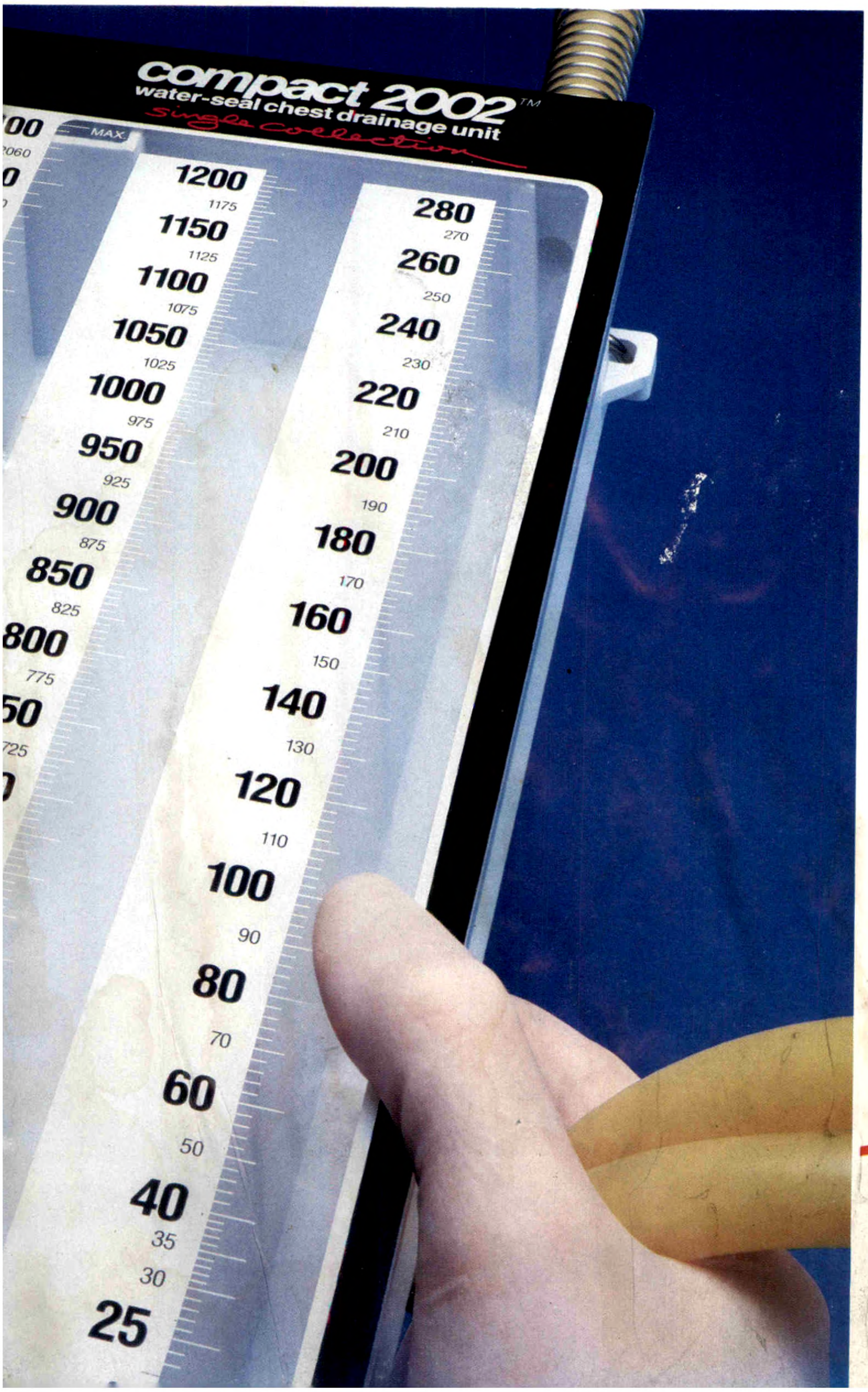

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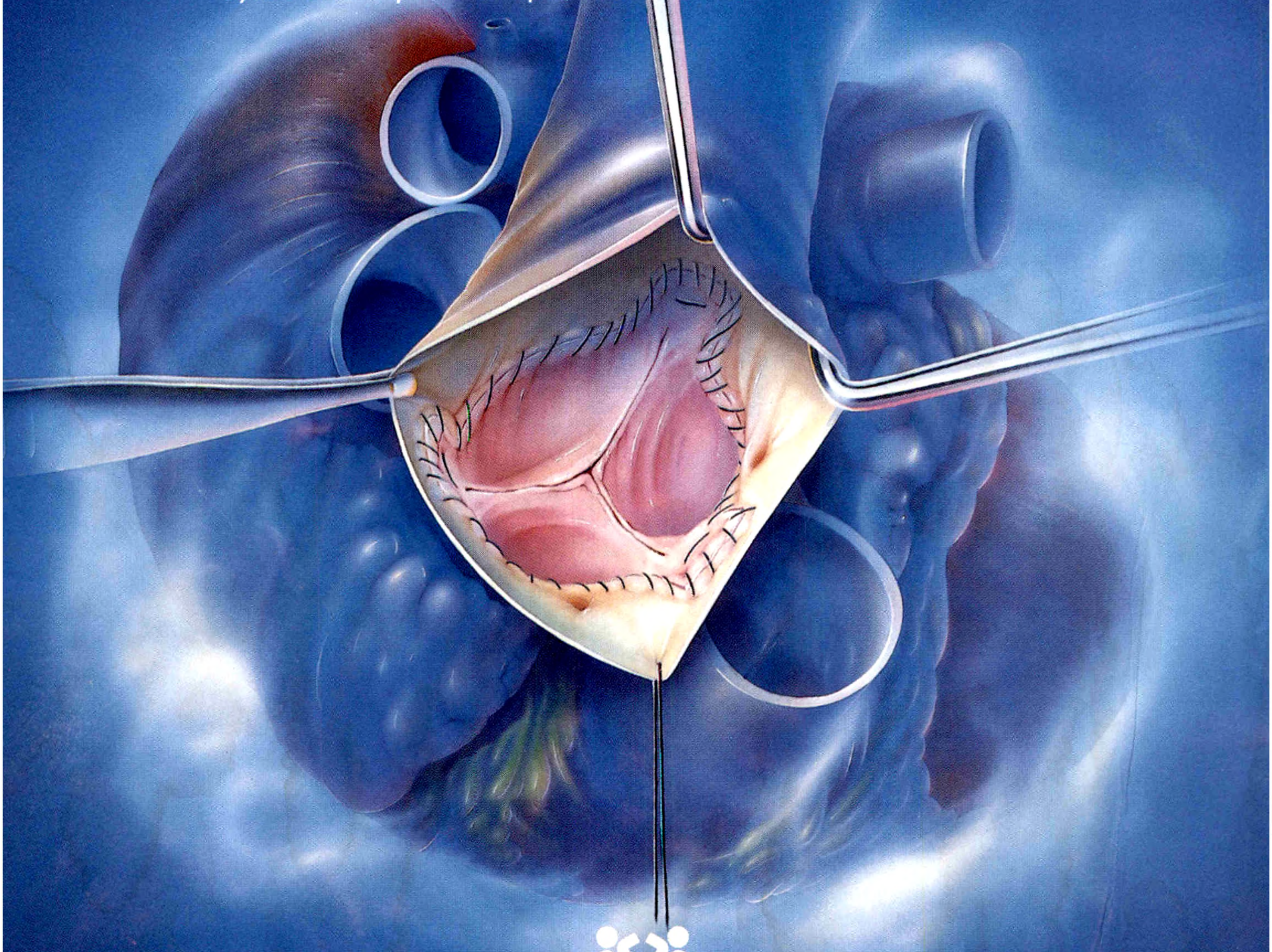

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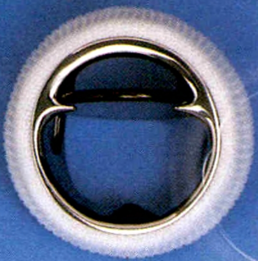

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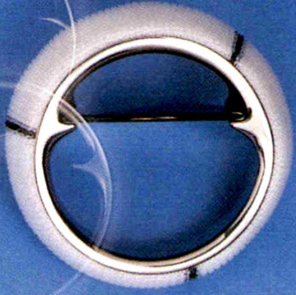

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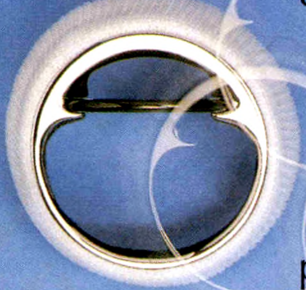

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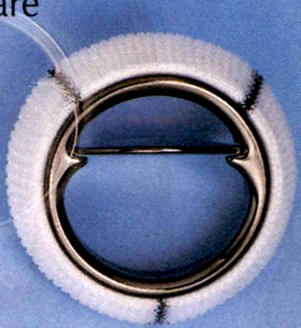

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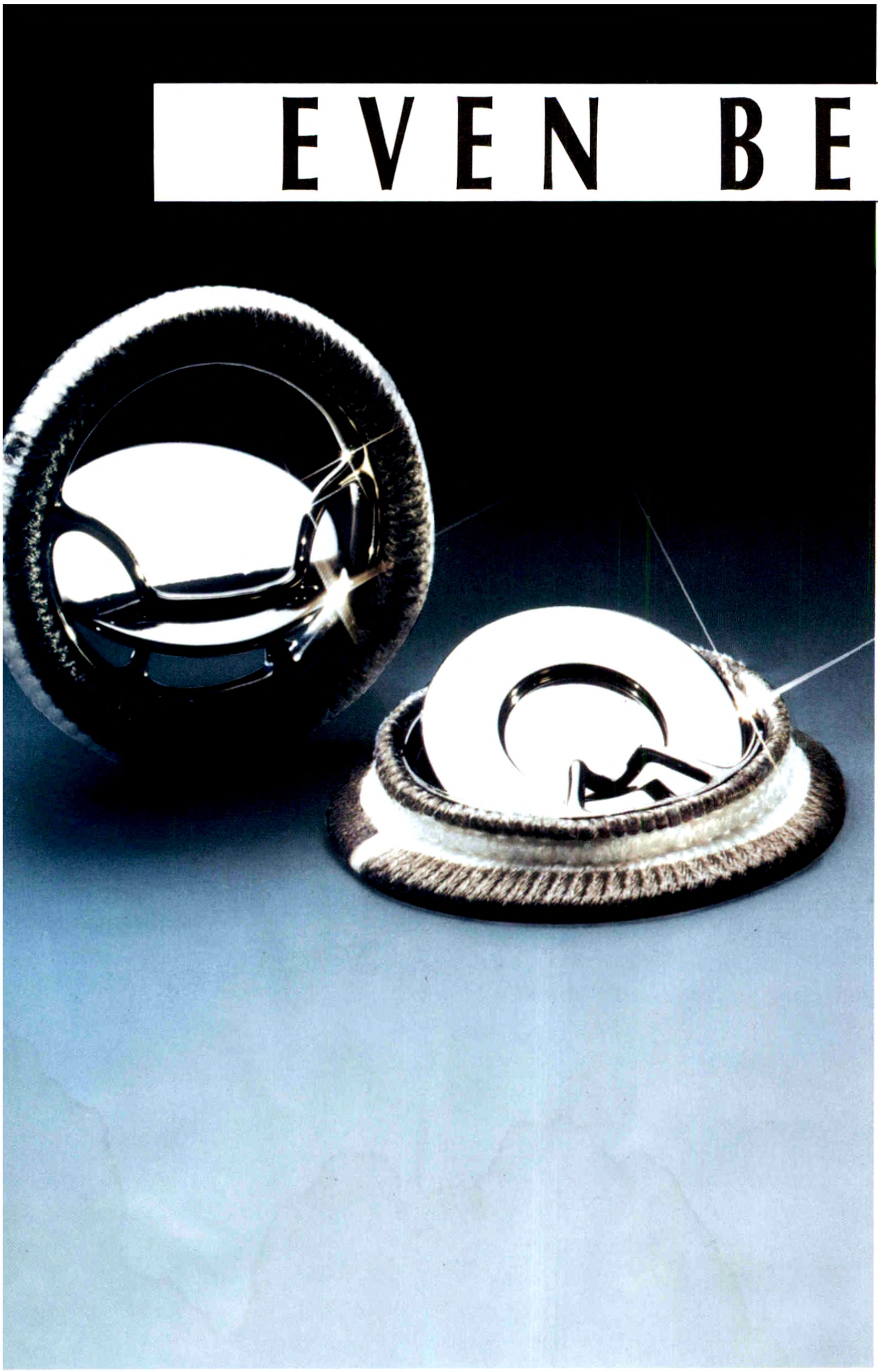

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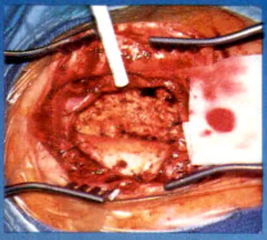

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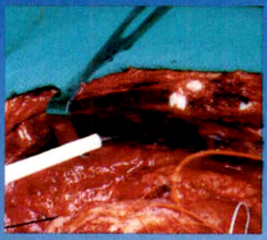

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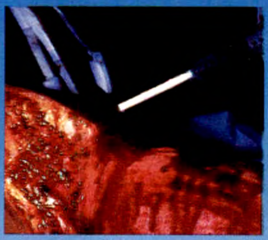

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PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

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3. In instances where THROMBOGEN* in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried THROMBOGEN* is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.
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   1. Prepare THROMBOGEN* solution of the desired strength.
   2. Immerse sponge strips of the desired size in the THROMBOGEN* solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
   3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

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Caution: Federal law prohibits dispensing without a prescription.

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The Pharmacological Treatment of Cardiovascular Diseases

Edited by

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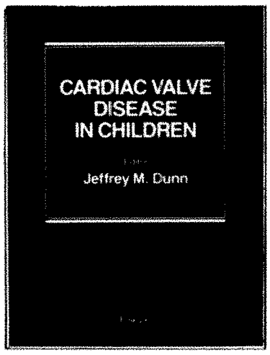

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DISEASE
IN CHILDREN

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About Viability in Valve Grafts

Norman E. Shumway, MD

Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, California

In this issue, Bodnar and associates [1] present an excellent review of the National Heart Hospital experience with aortic homografts in the subcoronary position. They rightfully conclude that long-term results are gratifying and patient survival satisfactory. Several methods of homograft preservation are assessed, and no significant difference can be found with respect to tissue failure, endocarditis, and event-free patient survival.

Bodnar and associates find no advantage in the use of so-called viable grafts over preserved homografts. Cryopreservation is currently the method of choice, patterned after the work of O'Brien and colleagues in Brisbane [2]. Cryopreserved grafts are, of course, commercially available and definitely nonviable.

In the early days of homograft valve replacement it was hoped that the homografts would share the immunological privilege of corneal transplants as neither is vascularized tissue. Only fresh valve homografts would be at any risk with respect to provocation of an immunological reaction, but as the degree of vascularization of the graft is minimal to absent, fresh grafts were not subjected even to blood type matching, let alone any more sophisticated analysis of tissue antigens. Accordingly, conclusions regarding the lack of any histocompatibility effect in this study were not unexpected.

Bodnar and associates speculate, "It is possible that none of the valves in our experience was truly viable." Actually, the only heart valves with any possibility of viability are those transplanted autologously. Donald Ross [3] is almost alone in the clinical application of an interesting laboratory exercise of pulmonic valve autotransplantation [4, 5]. In the normal dog the right ventricular outflow tract does not require a valve, but in the patient, especially one with pulmonary hypertension, the right ventricle must be reconstructed with some kind of valvular apparatus; hence, the patient seems always to be one valve shy after the autotransplantation.

One point not well developed by Bodnar and associates concerns reoperation after replacement of the aortic valve with a homograft. The entire homograft sleeve must be dissected away from the patient's natural aorta. Sharp dissection is a must because the homograft is firmly adherent to the subcoronary area. Simple removal of the failed valve cusps is not enough.

There is no perfect valve substitute, and Bodnar and associates are well aware of this fact. The only way a patient can escape a further valve operation actually is to die. Stated otherwise, if the patient lives long enough, he or she will undergo another valve operation.

Finally, beware of calf serum in the nutrient medium! Somehow Bodnar and associates have isolated calf serum from a myriad of variables as a factor in homograft valve longevity.

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The Malignancy of Large Cell Lung Carcinomas

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The epithelial lung tumors have a common ancestor in the simple, cuboidal endodermal cells of the primitive lung bud and, like any siblings, have overlapping characteristics. Names are given to these tumors by the World Health Organization based on their most pronounced light microscopic features, which promotes uniformity in diagnosis by stressing easily observed objective criteria. Biological differences occur in the tumors depending on the degree of development of various inherent cellular properties. Those that have scant cytoplasms, oval nuclei, finely distributed chromatin, and inconspicuous nucleoli are called small cell carcinomas. They have more pronounced endocrine properties than any group except the carcinoids, which are the most fully developed endocrine tumors of the lung. The classic small cell carcinomas (oat cells) are distinguished by pathologists from non-small cell carcinomas with a high degree of accuracy. Many oncologists are satisfied with this simple division because small cell carcinomas are more responsive to irradiation and chemotherapy than the others. But large cells with more abundant cytoplasm, more vesicular nuclei, and more prominent nucleoli may also be present, as well as squamous cells and gland-forming cells, so transitions exist between small cell tumors and non-small cell tumors.

When other inherent cellular attributes are sufficiently developed, they influence the biological and clinical behavior of the tumor. If it produces keratin or intercellular bridges (highly developed desmosomes) as seen in 5-μm sections, it is called a squamous cell carcinoma. Most of these arise centrally, have a long preclinical existence, exfoliate easily recognizable cells into the sputum, and invade adjacent structures, but are reluctant to metastasize. A few drops of mucin may be present but is regarded as a minor expression of genetic potential as behavior is not altered. If keratin and bridges are absent, but glandular structures or mucin in consequential amounts are present, the tumor is called an adenocarcinoma. Most of these are peripheral, are often associated with scarred lungs, and metastasize preferentially to the brain. They are the "coin" lesions discovered by roentgenographic examinations, are less apt to have positive sputa, and are often best diagnosed by fine needle aspiration.

What then is a large cell carcinoma? The term is used in two ways. It is used as a holding group for non-small cell carcinomas, which do not exhibit keratinization or gland formation on hematoxylin and eosin stain. This is particularly true of small biopsy specimens in which the sample is limited. In such cases the diagnosis may be changed to squamous cell carcinoma or adenocarcinoma when a larger sample is examined or mucin stains are done. Mucin stains alone will reduce the percentage of large cell carcinomas by a third. Grimelius stains will reveal that about 10% of large cell carcinomas have enough dense core granules to be classified among the endocrine tumors (malignant carcinoid or large cell carcinoma with endocrine features). When efforts to demonstrate keratin, bridges, mucin, and granules have failed, the definitive term *large cell carcinoma* is used, comprising about 10% of lung cancers.

The World Health Organization recognizes two subsets of large cell carcinoma: giant cell and clear cell. Giant cell tumors tend to be invaded by leukocytes, to have elevated white cell counts, and to be bulky when discovered. Survival is less than a year. Clear cell tumors are rare, and metastasis from a renal cell carcinoma must be ruled out. Most are actually areas of squamous cell or adenocarcinoma.

In their article in this issue, Downey and co-workers [1] have ruled out poorly differentiated squamous cell and adenocarcinoma, which contaminate most series. Grimelius stains would have identified a few tumors with endocrine features. Of 96 patients, 10 had clinical stage I lesions, with a median survival of 16 months after operation, at which time two were changed to pathological stage III. Over 90% of the tumors were clinical stage III or IV, with survival of 7.9 to 5.8 months after chemotherapy and/or radiotherapy. There are few good series with which to compare these results. At the University of Chicago, 48 large cell carcinomas were reported [2]. There were 6 patients with stage I tumors with a survival of more than 50 months and 5 patients with stage II tumors with a survival of 16.4 months. The patients with advanced stage tumors comprised 77% of the group, and had a survival of 7 to 10 months. Electron microscopic differentiation made little difference. If cellular features were not expressed by light microscopy, behavior did not appear to be influenced. In these series, 77% to 90% of large cell carcinomas were beyond stage II at the time of diagnosis; these patients survived for less than a year. This is of course worse than survival with squamous cell and adenocarcinomas.

Large cell carcinomas are undifferentiated and highly malignant tumors that consist of cells that may be the counterpart of the primitive endoderm. Such cells are present in practically all non-small cell carcinomas and in

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some small cell cancers. The spectrum of carcinoma of the lung may be represented by a Y, with two arms consisting of squamous cell cancers and adenocarcinomas, respectively, and the base consisting of small cell tumors such as carcinoids and small cell undifferentiated carcinomas. It is possible that the undifferentiated large cell carcinomas are at the fork of the Y at which there is dynamic interplay among the most malignant forms of all three basic types of lung cancer.

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Free Radicals: The Reperfusion Ninja

Andrew S. Wechsler, MD

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Twenty years ago McCord and Fridovich [1] discovered the endogenous free radical scavenger, superoxide dismutase. Since that time, investigators have contributed rapidly toward understanding the mechanisms that facilitate generation of free radicals in tissues and the biological neutralization of these oxidants. Fundamental to understanding free radical importance in cardiac surgery is the observation that rapid reintroduction of oxygen to ischemic tissues is only one of several potential mechanisms for free radical generation during cardiopulmonary bypass. Putative enzymatic events may generate substrate for free radical reactions that result in lipid, protein, and nucleic acid oxidations. Regional injury to the endothelium may act as a focus for further chemoactivation of leukocytes that in turn have been "activated" by events occurring during cardiopulmonary bypass. Activation may relate to complement-mediated interaction between blood and biomaterials. Other, and related, mechanisms invoke the xanthine oxidase–xanthine dehydrogenase system, mitochondrial enzymes, adenosine triphosphate catabolism, catecholamine oxidation, and free radicals emanating from arachidonic acid degradation.

Confusion exists regarding the sites and mechanisms of free radical generation in the setting of cardiac operations. The article in this issue by Menasché and Piwnica [2] organizes in a clear and understandable manner much of the current thinking. As one ponders the role of free radicals in myocardial injury, several important questions should be answered before it can be recommended that strategies to avoid free radical injury be applied in clinical practice. If myocardial protective techniques are rigorously applied, and if cell ischemia is thereby not equated with cell injury, does reperfusion cause generation of free radical oxidants? What fraction of reperfusion injury is free radical mediated? How much free radical injury is the consequence of systemic effects of cardiopulmonary bypass as compared with regional myocardial effects of ischemia and reperfusion? Is the experimental evidence convincing that dysfunction associated with reperfusion is associated with unequivocal evidence for free radical injury? Most of the biochemical assays that have been used to incriminate free radicals are nonspecific in their nature, and more precise methods for identifying effects of oxidants in tissues are required. Have studies suggesting beneficial effects of free radical "traps" and scavengers been properly controlled using rigorous, blinded techniques? Are we being unduly influenced by the greater probability that positive experimental results using such scavengers will be accepted for publication? Is reduction of oxidant injury likely to have a long-term effect on myocardial recovery, or is this a transient phenomenon? Finally, is there potential harm that could result from utilizing agents designed to interfere with free radical injury that have, themselves, been incompletely investigated?

Over the course of the next several years, it is anticipated that electron spin resonance spectroscopy will continue to be developed such that instantaneous detection, quantification, and identification of free radical species in intact organs will become possible [3]. These studies are anticipated to yield important confirmatory or contradictory evidence for the role of free radicals in myocardial injury. As Menasché and Piwnica [2] have indicated, the argument regarding the role of oxidant injury becomes more poignant as the nature of the cardiac surgical population shifts. Previous efforts to avoid ischemic injury were largely successful in minimizing perioperative dysfunction. The new patient substrate, operated on under conditions of ongoing ischemia, may be the catalyst for intensification of investigation into a mechanism of injury assuming progressively greater importance. Surgeons with a purely clinical approach should be careful not to accept, prematurely, preliminary data translated from laboratory experiments to the operating room. Controlled studies involving large numbers of patients need to be undertaken in a blinded manner before firm conclusions can be drawn.

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Viable and Nonviable Aortic Homografts in the Subcoronary Position: A Comparative Study

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One hundred fifty-five freeze-dried, 63 frozen, and 337 Hanks'–antibiotic solution preserved or nutrient–antibiotic solution preserved homografts used for isolated aortic valve replacement have been followed for 1 to 20 years (mean, 5.3 years), a total of 2,931 patient-years of follow-up information. Overall survival, valve-related death, primary tissue failure, failure due to surgical technical error, infective endocarditis, and overall event-free survival have been assessed and compared. Overall survival 20 years after operation was 51.6% ± 8.1% with a low incidence of sudden death. The method and length of preservation did not have any effect on the long-term performance or the mode of failure of the homografts. The rate of primary tissue failure was apparently higher with valves preserved in a solution containing calf serum, but the difference was not significant. It is concluded that long-term patient survival and quality of life after aortic valve replacement with a homograft are excellent. The current study, however, could not verify the existence of a significant difference between the three assessed methods of homograft preservation. Furthermore, it could not prove the importance of cellular viability or the existence of clinically significant immunological factors other than the calf serum content of the nutrient medium.

(Ann Thorac Surg 1989;47:799–805)

Aortic homografts have been inserted into the subcoronary position since 1962 [1, 2]. During the 1960s and early 1970s, the surgical application was extended to right ventricular outflow tract reconstruction [3], mitral and tricuspid valve replacement [4], and eventually replacement of the entire aortic root and valve [5]. Currently, homografts are mainly used for right-sided reconstructions. However, renewed interest is emerging in aortic valve replacement with a homograft, an operation that remained the most common indication for homograft insertion over the years at the National Heart Hospital, London.

The preservation of aortic homografts has seen major changes during the past quarter of a century. Clinical reports and experimental data are available on valves that have never been preserved (homovital) as well as on valves preserved by freeze-drying, freezing (current definition, cryopreservation), or storing at 4°C in Hanks' solution or in a tissue culture medium [2, 6–9].

The Homograft Department of the National Heart Hospital processed more than 5,000 valves between 1963 and 1988, and has implantation information on 2,869. A prospective randomized trial to compare different methods of preservation was never attempted. However, considerable numbers are present in each of the consecutive groups of freeze-dried valves (301), cryopreserved valves (476), and "fresh" valves stored in an antibiotic solution (2,092). Furthermore, more than 15 years have elapsed since the introduction of the latest major change (nutrient–antibiotic solution). It was therefore considered appropriate to assess and compare the three methods using a retrospective analysis of the accumulated clinical information. The results are the subject of this study.

Material and Methods

Selection Criteria

To obtain statistically comparable data, the following selection criteria were applied: (1) isolated aortic valve disease, (2) aortic valve replacement with a freehand-inserted homograft between January 1, 1963, and December 31, 1986, (3) processing of the homograft valves at the National Heart Hospital, (4) operations carried out at the National Heart Hospital, and (5) all operations done by the same surgeon (D.N.R.).

Clinical Material

Five hundred fifty-five hospital survivors qualified for the study. There were 398 men (71.7%) and 157 women (28.3%) (Table 1). The mean age was 40.5 ± 14.0 years. The indication for operation was stenosis in 175 patients (31.5%), regurgitation in 204 (36.8%), mixed aortic valve disease in 144 (25.9%), and failure of a previously inserted valve in 32 (5.8%) (Table 2). Follow-up ranged from 1 year to 20 years with a mean of 5.3 years. The total follow-up was 2,931 patient years.

The inserted valve was freeze-dried in 155 patients (27.9%), cryopreserved in 63 (11.4%), and fresh stored either in Hanks'–antibiotic solution in 77 (13.9%) or nutrient–antibiotic solution in 260 (46.8%). It was thought prudent to subdivide the so-called fresh valves, which were kept at 4°C, into two groups according to the basic solution used, ie, Hanks' or nutrient medium, because the latter contained fetal calf serum, a potent heterologous antigen.

Presented at the Twenty-fourth Annual Meeting of The Society of Thoracic Surgeons, New Orleans, LA, Sep 26–28, 1988.

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Table 1. Valve Type and Patient Data

Valve	No. of Patients	% Male	Age[a] (yr)
Freeze-dried	155	69.7	43.3 ± 13.3
Cryopreserved	63	69.8	41.3 ± 13.4
Hanks' 4°C	77	81.8	40.8 ± 14.0
Nutrient 4°C	260	70.4	38.6 ± 14.3
Total	555	71.7	40.5 ± 14.0

[a] Data are shown as the mean ± the standard deviation.

The freeze-dried valves were known to be nonviable. The fresh valves were regularly tested and found to contain a high cellular viability.

The source of valves was forensic or routine hospital autopsy, and the elapsed time between death and dissection of the valve was limited to 72 hours. Details of the respective methods of preservation have been published [6–9].

The surgical method of insertion was fixation of the homograft into the natural anatomical position with a proximal and a distal suture line without dissecting the noncoronary sinus. Details of the surgical technique have been published elsewhere [10].

Statistical Methods

Statistical assessment was carried out using the standard life-table method to calculate survival proportions and freedom from individual events [11]. The standard error of the difference between two actuarial proportions at any given cutoff point was calculated as defined earlier by our group [12]. The significance of the difference was ascertained using Student's t test. The formula of Cox and Lewis [13] for calculating the rate of constant terminating events was used to provide the so-called linearized rate of events as generally adopted, but these results were treated with skepticism if the occurrence of the event was not truly constant or random.

Ultimate failure of the valve was defined as death due to valve failure or surgical removal of the failed valve at reoperation if removal was necessitated by primary tissue failure or technical failure. Infective endocarditis was considered a terminating event irrespective of the occasional success of medical treatment. Hospital death after reoperation was considered a valve-related death.

Table 2. Valve Type and Clinical Diagnosis

Valve	Stenosis No.	Stenosis %	Incompetence No.	Incompetence %	Mixed No.	Mixed %	Reoperation No.	Reoperation %
Freeze-dried	66	42.6	54	34.8	34	21.9	1	0.6
Cryopreserved	26	41.3	20	31.7	16	25.4	1	1.6
Hanks' 4°C	21	27.3	37	48.1	15	19.5	4	5.2
Nutrient 4°C	62	23.8	93	35.8	79	30.4	26	10.0
Total	175	31.5	204	36.8	144	25.9	32	5.8

Primary tissue failure included attenuation, shrinkage, rupture, and extrinsic or intrinsic calcification. Technical failure was indicated if the incompetence, usually early, was clearly caused by incorrect insertion. Infective endocarditis was diagnosed if positive blood cultures, progressive anemia, and splenomegaly were present. Echocardiography was instrumental in several instances. With the exception of patients who responded to medical treatment, the diagnosis was confirmed at reoperation or by autopsy.

Thrombosis, embolism, pathological bleeding, and hemolysis were assessed but not entered into the statistics, as none of these events were observed during follow-up in this group of patients.

The cumulative event-free survival encompasses freedom from structural failure (primary tissue failure), surgical technical problems, infective endocarditis, thrombosis, embolism, anticoagulant-related bleeding, and hemolysis whether reoperation was performed or not. It is, therefore, a cumulative and comprehensive assessment of device failure and treatment failure.

Statistical comparisons between the methods of homograft preservation were completed by applying a 10-year censoring point to each group, although the maximum available follow-up was 20 years with freeze-dried valves, 18 years with cryopreserved valves, and 16 years with the fresh group of valves. In this way, the total follow-up information was decreased by 311 years to 2,642 years. Both the amount of remaining follow-up data and the length of the 10-year follow-up were considered adequate to assess the potential differences, yet the significance levels were not undermined by the subsequently decreasing numbers at risk.

Results

Overall Performance Indices

LATE DEATH. Eighty-one patients died during the 20-year follow-up, 68 of them within the first 10 years. The linearized rate of death was 2.73% ± 0.31% for the 20-year follow-up, 2.57% ± 0.31% for the first decade and 4.19% ± 1.16% for the second decade. The annual rate of death ranged between 1% and 4% during the first decade and between 0% and 11% during the second decade. It was, therefore, neither constant nor random, and so did not comply with the original criteria of Cox and Lewis [13]. For this reason, statistical comparison was not attempted from this set of data, and the following alternative was applied instead.

The distribution of the causes of death is summarized in Table 3. Although the percent distribution of the first 10-year period can be considered as representative of the entire follow-up, the proportion of valve-related deaths increased significantly during the second 10-year period ($p < 0.05$). No other significant changes were found.

VALVE FAILURE. There were 210 instances of fatal or nonfatal valve failure, 167 of them occurring during the first 10 years of follow-up. The linear rate of the event was not calculated because the annual rate of valve failure increased substantially after the first 7 to 8 years but

Table 3. Causes of Death

	Years of Follow-up					
	1–10		11–20		1–20	
Cause	No.	%	No.	%	No.	%
Valve related	35	51.5[a]	9	69.2	44	54.3
Cardiac related	11	16.2	1	7.7	12	14.8
Sudden	2	2.9	1	7.7	3	3.7
Other	10	14.7	1	7.7	11	13 6
Unknown	10	14.7	1	7.7	11	13.6

[a] Significance: $p < 0.05$.

decreased to 0% after 18 years. The cumulative actuarial proportion of freedom from valve-related death, any valve-related complication, or both, after 5, 10, 15, and 20 years was 77.87% ± 2.17%, 45.57% ± 3.04%, 21.59% ± 3.29%, and 9.00% ± 3.53%, respectively.

Comparison of Methods of Preservation

Overall survival and freedom from valve-related death were significantly worse with freeze-dried valves than with any other type of valve ($p < 0.05$) (Figs 1, 2). However, this was not caused by factors related to the patient population or to the mode of valve failure, which would separate this group from the others. Historically, freeze-dried valves were the first clinical series of homografts inserted and therefore, the first requiring reoperation. The mortality associated with reoperation in this early series was twice as high as that experienced later (Table 4). In addition, stringent protocols aiming at the early diagnosis and treatment of infective endocarditis were not available in those days. This factor also increased the late mortality.

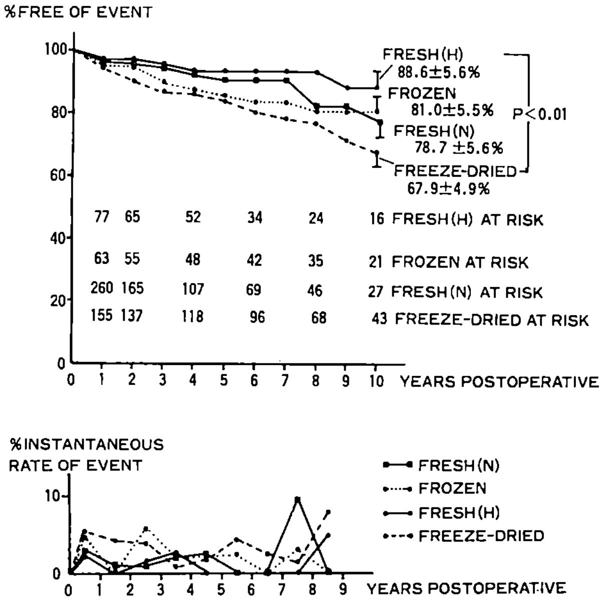

Fig 1. Comparison of overall survival after aortic valve replacement with freeze-dried, fresh, and cryopreserved homografts. (H = Hanks'; N = nutrient.)

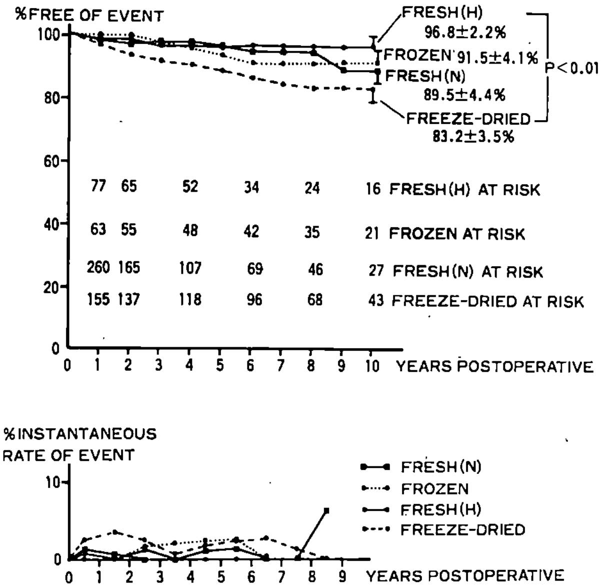

Fig 2. Comparison of freedom from valve-related death after aortic valve replacement with freeze-dried, fresh, and cryopreserved homografts. (H = Hanks'; N = nutrient.)

Surgical technical error was evenly spread among the four groups. Ninety percent of the patients were found free from this event after 10 years (Fig 3).

Infective endocarditis occurred at a fairly constant rate in each group. The linearized rates (in patient-years per annum) were as follows: freeze-dried 1.38 ± 0.38; cryopreserved 0.73 ± 0.42; Hanks'–antibiotic solution, 1.30 ± 0.58 and nutrient–antibiotic solution, 0.92 ± 0.33. The differences were not significant. The actuarial proportions of freedom from this event did not show a significant difference either (Fig 4).

Primary tissue failure had an identical pattern in each group. It became apparent after the first 3 years and started accelerating after 7 to 8 years (Fig 5). There is a 10% to 11% difference between the valves stored in a nutrient–antibiotic solution and all other valves; however, this difference is not significant. Nevertheless, it is worth noting that these fresh valves, and they alone, were kept in a solution containing 10% fetal calf serum. It was proven recently that the calf serum content of the homograft valve can act as a potent heterologous antigen [14].

Freedom from all valve-related events ranged between

Table 4. Reoperations Within 10 Years

Valve	No. of Reoperations	Died	Mortality (%)
Freeze-dried	59	12	20.3
Cryopreserved	20	1	5.0
Hanks' 4°C	22	2	9.1
Nutrient 4°C	51	6	11.8
Total	152	21	13.8

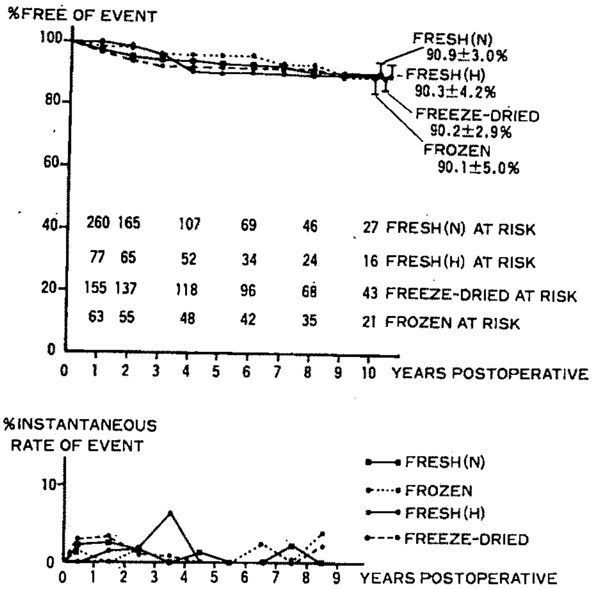

Fig 3. Comparison of freedom from technical failure after aortic valve replacement with freeze-dried, fresh, and cryopreserved homografts. (H = Hanks'; N = nutrient.)

41.1% for valves stored in nutrient–antibiotic solution and 50.4% for cryopreserved (frozen) valves, but the difference was not significant (Fig 6).

Early tissue failure was not observed in any of the four groups. This finding strongly contradicts the hypothesis that immunological factors would have an important impact on the long-term performance of homograft valves.

Comments

The medical literature has very few publications concerning prospective randomized trials with replacement heart valves. With homografts, to our knowledge, there are none.

Historically, of the first two homografts inserted into the subcoronary position, one was preserved by freeze-drying [1], whereas the other was a homovital valve [2]. In

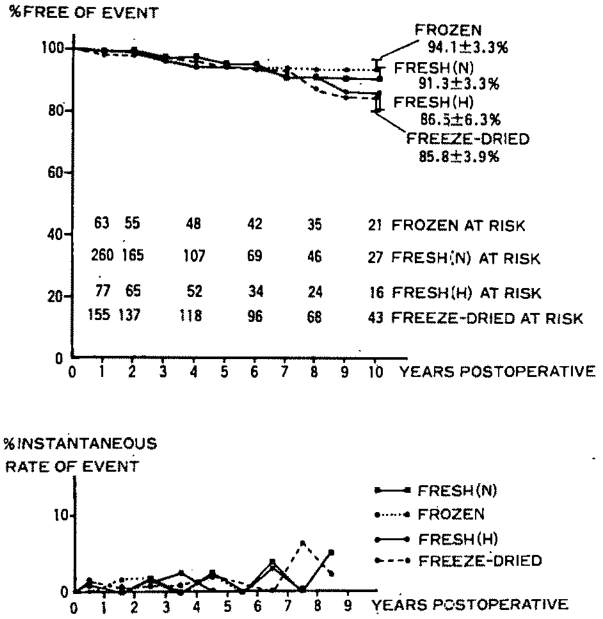

Fig 4. Comparison of freedom from infective endocarditis after aortic valve replacement with freeze-dried, fresh, and cryopreserved homografts. (H = Hanks'; N = nutrient.)

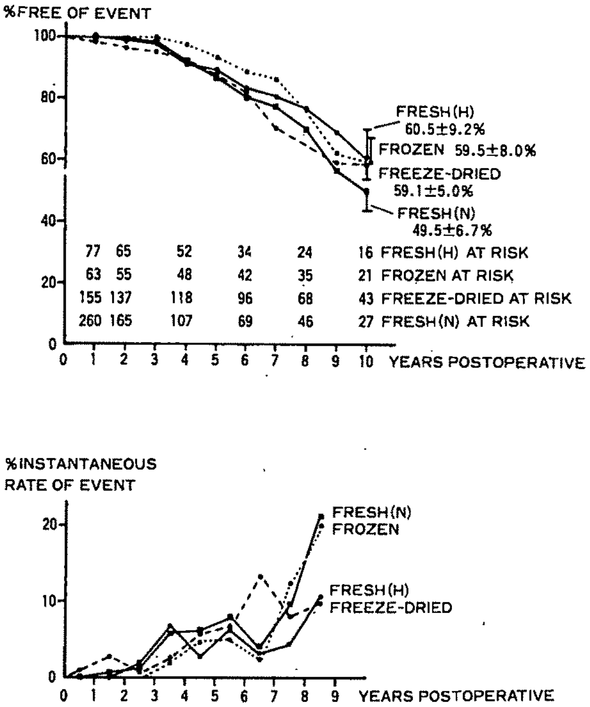

Fig 5. Comparison of freedom from primary tissue failure after aortic valve replacement with freeze-dried, fresh, and cryopreserved homografts. (H = Hanks'; N = nutrient.)

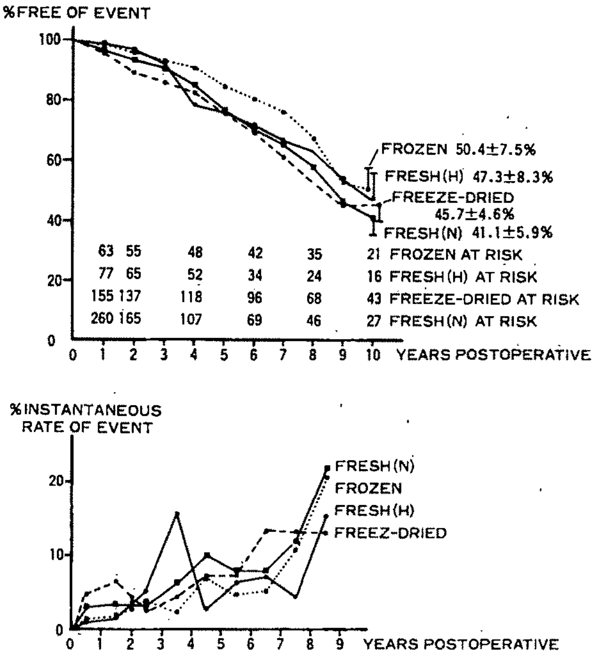

Fig 6. Comparison of freedom from valve-related death and all valve-related complications after aortic valve replacement with freeze-dried, fresh, and cryopreserved homografts. (H = Hanks'; N = nutrient.)

this truly pioneering era of heart surgery, neither of the two methods was tested and assessed in vitro or in vivo as to their respective suitability for homologous heart valve preservation. The ease of storage and the accumulated experience in the application of lyophilization to store other human tissues, especially blood vessels, provided the rationale to adopt freeze-drying for the first large clinical series of homograft valves [6].

Disappointing long-term results with freeze-dried arterial segments as well as reports on homograft valve failures prompted the introduction in 1968 of freezing using dimethyl sulfoxide as a cryopreservative followed by storage in liquid nitrogen at −196°C [7]. Before long-term results with cryopreserved valves became available and meaningful comparisons could be made, the concept of cellular viability emerged, and the method of its maintenance in a tissue culture medium was proposed [15]. Cryopreservation, like freeze-drying, was abandoned. Its potential was reassessed and the method reintroduced in 1975, but until recently, cryopreservation of homograft valves remained limited to one center [16]. Currently, the majority of homografts are cryopreserved. Some hospital laboratories prefer storing valves in the traditional Hanks' or nutrient–antibiotic solution at 4°C, and there are a few centers that use homovital valves.

The results of our study did not demonstrate any difference in durability or in any of the other clinical performance indices between homografts preserved by freeze-drying, cryopreservation, or storing in a nutrient solution at 4°C. The importance of this observation is underlined by the fact that the freeze-dried valves did not contain viable cells. The other groups were, and the cryopreserved valves still are, declared and accepted as containing viable cells. The consequence is a simple conclusion. Either cellular viability is not preserved permanently by any one of the methods assessed, or permanent cellular viability does not have any effect on long-term performances of the homologous heart valves, or both of these statements are true.

The argument against this might be that the study is not based on a prospective randomized trial, or that there were some overriding factors present in each group diminishing the potential differences that were due to the methods of preservation.

The validity of a retrospective assessment such as the present report depends on several factors. The most important single one is the effect of the different time frames involved. This is clearly demonstrated by the high mortality associated with reoperation and infective endocarditis within the freeze-dried group compared with the others. The early time frame, however, did not have any effect on the time-related occurrence of primary tissue failure, infective endocarditis, or surgical technical problems, as shown by the relevant event-free survival curves.

Of the potential overriding factors, the 24- to 72-hour interval between the donor's death and the dissection of the valve seems to be the only one to cause concern. None of the valves assessed by this study were harvested from "beating-heart donors" or in any way as part of a transplant procedure. The hearts were removed during forensic or routine hospital autopsy 12 to 48 hours after death, and dissection of the valve commenced within the next six to 24 hours.

Our own laboratory results [9] as well as those of others [15] have demonstrated a high percentage of viable fibroblasts in valves of cadaveric origin. The great many efforts over the years were aimed only at preservation of the viability present 24 to 72 hours after death. It may well be that all those efforts have failed, as suggested by the results of McGregor and associates [17], who found a total disappearance of cellular viability within 21 days in valves stored in nutrient–antibiotic solution.

However, the same group [18] completed an elegant series of animal experiments that provided strong evidence that homovital valves, with a demonstrably high cellular viability, provoke a strong immunological reaction and deteriorate faster than the nonviable valves. More recent studies [19] using histocompatibility assays concluded that the antigen expression of human valvular tissue is localized mainly to the endothelium and declines rapidly during the first 48 hours after death.

It seems relevant to compare results published in the medical literature obtained with cryopreserved valves, some collected from transplant procedures and some as mortuary material. Long-term results published by O'Brien and colleagues [16] demonstrated a total lack of calcification and only occasional late tissue failure in cryopreserved valves followed for a 12-year period, whereas in the clinical report of CryoLife, Inc, early tissue failure as well as early calcification is presented, although the method of preservation is basically the same as that of O'Brien [16]. There are, however, two differences between these two groups of cryopreserved valves that seem important and pertinent. One is that CryoLife used bovine serum in the preserving medium; O'Brien never did. The other is that CryoLife processed and stored valves from beating-heart donors, whereas O'Brien's published clinical experience was limited to mortuary valves.

Both differences relate to the potential role of immunological factors determining the long-term performance of aortic homografts. The present study can neither prove nor contradict this hypothesis because it could not ascertain the existence of clinically important immunological factors. It is possible that none of the valves in our experience was truly viable and that this eliminated all major antigen expression. The apparently highest rate of primary tissue failure in valves treated in a calf serum–containing medium may be interpreted as a sign of rejection of the heterologous antigen, but the difference is nonsignificant.

Our recent experiences make the problem even more complicated. Cryopreservation was reintroduced at the National Heart Hospital in 1983 and was used parallel to nutrient–antibiotic solution preservation until January 1988. Since then, cryopreservation has been *the elective* method because of the unlimited storage period it provides. None of these cryopreserved valves have failed to date. However, there has not been any failure reported with any of the nutrient–antibiotic solution–preserved valves inserted during the same period either. It is obvious that a much longer follow-up is necessary before meaningful comparisons can be made relating to these valves inserted during the last 5-year time frame.

In conclusion, it is suggested that the assessment of long-term clinical performance of aortic homografts in the aortic position could not demonstrate any difference between the preservation methods used over the past 25 years. The presence or absence of cellular viability as assessed by accepted laboratory methods did not have any effect on the clinical results. Our data question the continuing presence or the importance of viable cells in the inserted homograft.

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DISCUSSION

DR DAVID R. CLARKE (Denver, CO): I congratulate the authors on a very interesting and thought-provoking study, and congratulate Dr Bodnar on an excellent presentation. I thank him for providing me with a copy of the manuscript well in advance of the meeting for my review.

If one were to prospectively predict the results of this study, it would be difficult to imagine that valves prepared by such markedly different processes would 10 years later show identical results. There are, however, two scenarios that could explain this phenomenon.

One possible situation is that, as Dr Bodnar suggested, all of the valves were substantially nonviable at the time of implantation. This is not hard to fathom because it is known that freeze-dried tissue is nonviable. It is also known that valves stored at 4°C, with or without nutrient medium, last just a few days, and cryopreservation in 1968 may not have been exact enough to guarantee cell viability.

I have a couple of questions for Dr Bodnar in this regard. Was there any viability testing at the time of implantation or any evidence for or against donor cell viability at explantation of any of the valves? What was the average time between donor death and implantation, particularly in the groups where storage at 4°C was used?

Recipient immunological responses, which might likely increase with greater degrees of viability, could result in tissue degeneration, despite some ability to resist mechanical wear and tear. This could conceivably provide the second scenario leading to these results. This might also explain, as Dr Bodnar mentioned in his manuscript, the increased variability of the duration of valve survival in the cryopreserved series, even though at 10 years the results were the same, and would also correlate well with the slightly worse results observed in the valves that were soaked in fetal calf serum. In this regard, I wonder if ABO compatibility was examined, whether other immunological studies were conducted, and whether the histology of any explanted valves showed any evidence of an immunological phenomenon.

Mark O'Brien from Brisbane, Australia, has reported a series of cryopreserved allografts compared with a series of fresh, although nonviable, allografts. The patient survival curves are very similar to those in this series. The freedom from thromboembolism is similar between the cryopreserved and the fresh, nonviable allografts, and freedom from endocarditis is virtually identical out to 10 years. However, if we look at overall actuarial valve survival or valve freedom from all complications, we see that the cryopreserved allografts are performing significantly better at slightly over 10 years.

Dr Bodnar, can you suggest a reason for the apparent conflict between these data from Australia and your own?

DR BODNAR: Dr Clarke, thank you very much for your kind comments. I used the expression, the valves were "thought" to be viable at the time of insertion, because the available method, radioactive thymidine uptake, showed them to be viable. Later studies contradicted those results. Therefore it is very difficult to say whether they were or were not viable. According to the contemporary method of assessing viability, they were "viable" valves at implantation.

This viability was recorded when the valves were dissected and then followed for up to 8 weeks of preservation in the nutrient solution. It was decreasing with time but never became less than 40%. The average time of valve storage has not been recorded, but the valves were never kept for longer than 6 weeks.

The viability was sometimes tested at implantation—not routinely—and sometimes it was assessed if the valve was explanted. Some early explanted valves did contain viable cells, but as a rule, we do not find viability in valves that necessitate reoperation.

Here I would refer to the presence of immunological factors. We could not prove by histology, immunofluorescence, or other methods the presence of immunological factors on the surface or within the layers of these homografts. ABO group matching was done at the early stages. It did not seem to have any relevance to long-term clinical results.

As far as Mark O'Brien and his series is concerned, I state first that I admire him, and I believe everyone does, for the excellent results he achieved with homografts. I believe these results are incomparable with those obtained with any other valves in medical history.

However, he started cryopreservation in 1975. The valves I described were from 1968 and 1969. The importance of the time frame is underlined by our experience that during the past 5 years, we did not experience any primary tissue failure whether the valve was fresh or cryopreserved. However, we think it is inappropriate to use such short-time experiences to make judgments on important issues.

There are other differences, which may be inherent in the patient material itself. Dr O'Brien saw a considerable number of thromboembolisms, which we never see in London. There has not been one in the group I just presented, and among all of those homografts for which we have follow-up information, there has been only one transient embolism.

Finally I suggest that these excellent results, which we admire, are unique to Dr O'Brien whereas cryopreservation is not. Others using cryopreserved valves could not reproduce those results, nor could we. Therefore I am afraid there is still no final answer to these questions of preservation.

Important Notice From The Society of Thoracic Surgeons

Annual Meeting Changes

After extensive deliberation, the Council voted unanimously to return the time of the annual meeting to the January–February period beginning in 1991. The following dates and places have been selected by the Council.

25th Annual Meeting
September 11–13, 1989
Baltimore, Maryland

Interim Meeting
September 21–23, 1990
Chicago, Illinois

26th Annual Meeting
February 18–20, 1991
San Francisco, California

The interim meeting of September 22–23, 1990, will resemble that of the very successful interim meeting held in Dallas, Texas, January 30–February 1, 1987. Many members have requested that this format be repeated. In addition to its scientific component, this meeting will emphasize the socioeconomic aspects of cardiothoracic surgical practice, issues that currently require extensive time and effort by the Council and committees of The Society. The 26th Annual Meeting in February 1991 will have the usual annual meeting format.

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Large Cell Carcinoma of the Lung: A Highly Aggressive Tumor With Dismal Prognosis

Richard S. Downey, MD, C. Whitaker Sewell, MD, and Kamal A. Mansour, MD

Division of Thoracic and Cardiovascular Surgery, The Joseph B. Whitehead Department of Surgery, and Department of Pathology, Emory University School of Medicine, Atlanta, Georgia

A retrospective review was made of 96 consecutive patients with large cell carcinoma of the lung admitted to Emory University Hospital over 10 years. Only 10 patients were seen with stage I lesions favorable for resection. The remainder were treated primarily with irradiation or chemotherapy. Mean survival for clinical stage I patients was 15.9 months; stage IIIA patients, 7.9 months; stage IIIB patients, 7.1 months; and stage IV patients, 5.8 months. Only 1 patient survived for 5 years. This distinct and highly aggressive form of lung cancer most commonly is seen at an advanced stage and is associated with an unusually dismal prognosis regardless of the method of treatment employed.

(Ann Thorac Surg 1989;47:806–8)

Of the histological variants of lung cancer, large cell is infrequently encountered, representing about 10% of large series of bronchogenic carcinoma. Because of this low incidence, controversy continues over the prognosis for patients with this tumor, particularly in relation to other types of lung cancer. Five-year survival has been reported to range from less than 10% [1] to more than 50% [2, 3]. The role of therapeutic intervention in these patients has been incompletely elucidated. To clarify the natural history of this tumor and to assess the contribution of various methods of treatment and survival characteristics, we reviewed the Emory University Hospital experience with all patients admitted with a diagnosis of large cell carcinoma of the lung over a 10-year period.

Material and Methods

The hospital records of 96 consecutive patients admitted to Emory University Hospital between 1973 and 1983 with the diagnosis of large cell carcinoma of the lung were retrospectively reviewed. This group accounts for 6.7% of all patients with carcinoma of the lung admitted during those years. All patients were followed until death or December 1987. Follow-up was complete for 100% of the patients. Only 2 patients were alive at the time of review.

The neoplasms were examined by light microscopy using hematoxylin and eosin stain and either mucicarmine or Alcian blue stain to detect production of mucus. Those tumors showing focal mucin positivity were reclassified as poorly differentiated adenocarcinoma.

Histologically, large cell carcinomas characteristically grow in sheets without organization or pattern and thus have no differentiating features [4]. Tumors with areas of squamous differentiation, including keratinized cells, squamous pearls, and intercellular bridges, are excluded. Similarly, gland formation and mucin-producing cells should not be present, nor should cells that fit size and nuclear criteria of small cell carcinoma. The World Health Organization criteria [5] require that giant cell carcinoma and clear cell carcinoma be classified as variants of large cell carcinoma.

Results

Among the 96 patients, there were 67 men and 29 women with a mean age of 61.5 years (range, 38 to 89 years). Ninety-two patients (96%) were cigarette smokers. Symptoms at presentation were nonspecific, and most commonly included cough (21 patients, 22%), weight loss (18 patients, 19%), and shortness of breath (17 patients, 18%). There were a variety of other, less common complaints (hemoptysis in 11, bone pain in 10, superior vena caval syndrome in 3, central nervous system symptoms in 7, and other, less specific complaints in 36). Nine patients (9%) were asymptomatic, and 4 of them were found to have stage I disease.

The histological diagnosis of large cell carcinoma was established by bronchoscopy in 35 patients (37%), mediastinoscopy or parasternal mediastinotomy, or both, in 21 patients (22%), thoracentesis in 6 patients (6%), thoracotomy in 14 patients (15%), computed tomography–directed needle biopsy in 13 patients (14%), and biopsy of adrenal gland, brain, or bone in the remaining patients.

All pathological specimens were reviewed by the Emory University Hospital Department of Pathology, and the diagnosis of large cell carcinoma was established by the criteria already outlined. At the time of chart review, pathological slides of patients surviving for more than 1 year were reexamined to confirm the diagnosis of large cell carcinoma.

Clinical staging using the TNM classification [6] was established for all patients at the time of diagnosis. All patients underwent routine chest roentgenography and then further radiographic or invasive evaluation as indicated. Ten patients were in clinical stage I, 31 were in stage IIIA, 34 were in stage IIIB, and 21 were in stage IV. None of our patients could be classified as stage II.

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Table 1. Treatment by Preoperative Stage

Preop Stage	No. of Patients	Operation	Irradiation	Irradiation and Chemotherapy	Chemotherapy	None	Operation and Irradiation
I	10	8	2	0	0	0	0
II	0	. . .	. . .	. . .	. . .	. . .	. . .
IIIA	31	0	22	0	6	2	1
IIIB	34	0	19	1	7	5	2
IV	21	1	14	1	3	1	1

Treatment of each patient was determined by stage at presentation (Table 1). Of those classified as stage I, 8 underwent thoracotomy, 7 having lobectomy and 1, pneumonectomy. The remaining 2 stage I patients were treated with external-beam irradiation because of poor pulmonary function tests. Pathological evaluation of operative specimens resulted in a postoperative change for 2 stage I patients to stage III.

Of the 31 patients classified as clinical stage IIIA, 22 underwent radiation therapy and 6, chemotherapy. One received a combination of treatments, and 2 were given no treatment. Nineteen stage IIIB patients received radiation therapy, 7 received chemotherapy, 5 had no treatment, and 3 had a combination of therapies. Of the 21 stage IV patients, 14 were treated with radiation therapy, 3 with chemotherapy, and the remainder with a variety of methods (see Table 1).

Survival data are shown in Table 2. A p value of less than 0.05 between means was accepted as significant. Mean survival for all stage I patients was 15.9 months (range, 1 month 9 days to 42 months 7 days). Three patients survived for more than 2 years, but none survived for 5 years. Because of the small number of stage I patients, statistically valid conclusions about the relationship between various methods of treatment and survival could not be made for this group.

Stage III patient survival was similarly poor. Survival was not significantly different between stage IIIA and IIIB patients (mean survival, 7.9 versus 7.1 months, respectively) when the 2 stage IIIB patients alive at the time of review were excluded. (One survived for 4.5 years and the other, 6.8 years). Inclusion of these patients in the data changed Stage IIIB survival to 10.7 ± 2.9 months (mean ± standard error of the mean), again not significantly different from stage IIIA survival. Five stage IIIA patients survived for 2 years, and only 1 survived for 5 years.

Stage IV patients also did not fare well, as shown by a mean survival of 5.8 months after diagnosis. Six stage IV patients survived for 2 years, but none survived for 5 years.

Survival was not significantly influenced by the type of adjuvant therapy used (see Table 2). Neither irradiation nor chemotherapy had a beneficial effect. However, because the number of patients in each treatment group is small and these therapies were not given in a randomized fashion, we do not think definitive conclusions about the efficacy of these treatments can be obtained from our data.

Comment

Because large cell carcinoma of the lung accounts for only about 10% of the experience of most authors, limited data about this tumor have been reported. Consequently, the natural history of the tumor and its implications for patient survival are subjects of considerable controversy. In our patients, the diagnosis of large cell carcinoma was almost uniformly associated with death in less than 9 months for patients with stage III tumors. Modest prolongation of survival to approximately 16 months was found only in patients with stage I disease. The aggressive nature of this tumor is further evidenced by the stage at diagnosis. Only 10% of patients were seen with stage I disease; the remaining 90% were found to have either stage III or IV disease when diagnosed.

Recognizing the inherent limitations of this retrospective review, we found little difference in survival with various treatment methods. Both radiation therapy and chemotherapy produced no significant improvement in stage IIIA or IIIB patient survival. Three stage I patients

Table 2. Patient Survival[a]

Stage	No. of Patients	Overall	Radiation Therapy	Chemotherapy	No Therapy
I	10	15.9 ± 4.9	. . .	. . .	. . .
II	0	. . .	. . .	. . .	. . .
IIIA	31	7.9 ± 1.6	7.8 ± 1.5	8.3 ± 6.0	. . .
IIIB	32[b]	7.1 ± 1.3	7.8 ± 1.9	8.6 ± 4.6	3.0 ± 2.2
IV	21	5.8 ± 0.9	4.5 ± 1.0	10.7 ± 1.4	. . .

[a] Data are shown as the mean ± the standard error of the mean in months.

[b] This excludes 2 patients alive at the time of review. See text for further details.

survived for more than 2 years, and all had been treated with lobectomy. Two of these patients were found to have nodal involvement requiring postoperative reclassification to stage III.

Previous reports describing the prognosis for patients with this tumor have contained varying data. Five-year survival ranged from 5.9% to 66% [1–3, 7]. Such discrepancies could be due to several factors. Small numbers of patients with large cell carcinoma in all series make accurate determinations of survival difficult. In addition, some series such as that from the Mayo Clinic [3] describe only early-stage patients whose survival would be expected to be favorable. However, such a large series [3] of patients with stage I large cell carcinoma is distinctly unusual, and strict criteria for the histological diagnosis of large cell carcinoma must be rigidly applied in such instances to exclude patients with large cell squamous carcinoma or large cell adenocarcinoma, which have a more favorable prognosis.

Furthermore, some authors [7–10] group large cell carcinoma with other histological types of poorly differentiated tumors, such as small cell or adenocarcinoma, because of superficially similar histological appearance, degree of differentiation, or presumed biological behavior. Such mixing, however, obscures the specific characteristics of large cell histology, and estimated survival may consequently be overly optimistic. Current treatment protocols for small cell cancer have dramatically changed the outlook for patients with this tumor in recent years, thereby further emphasizing the need to differentiate between large cell cancer and these lung tumors.

As expected, the best prognosis for patients with large cell cancer occurs in those with limited-stage disease. These tumors are, by definition, the most amenable to resection. Postoperative 5-year survival has been reported in the range of 20% to 30% [1, 7, 10]. Patients with stage I disease have been shown by one group [3] to have a survival of up to 66%. Lymph node metastases generally connote a much poorer prognosis. Rubinstein and colleagues [2] reported a decrease in 5-year survival from 52% if the nodes were negative to only 10% if the nodes were positive.

Despite newer adjuvant therapeutic protocols effective against both small cell and epidermoid cell lung cancer, the only currently available hope for patients with large cell carcinoma is early diagnosis followed by complete surgical resection. For patients with early-stage tumors, 5-year survival of up to 20% has been reported, which is comparable with that for patients with squamous cell and adenocarcinoma of similar stage [7–9]. In fact, Martini and associates [8] claimed that "once identified as a non-oat-cell tumor, the specific histologic variant (resectable patients) does not seem to influence survival."

Our data are at variance with those in previously reported series. Even patients with stage I disease had a limited prognosis regardless of the therapeutic intervention employed. We had only a single 5-year survivor, and survival for all stages was significantly worse than previously reported for either squamous cell carcinoma or adenocarcinoma. We believe that large cell carcinoma is a distinct and highly aggressive form of lung cancer, and that its diagnosis portends a very poor prognosis regardless of stage. The majority of patients are seen with an advanced tumor, and this makes cure and long-term survival not possible. Even for patients with early-stage lesions, survival continues to be dismal despite aggressive surgical resection and use of adjuvant therapeutic methods.

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Enhanced Myocardial Protection With Adenosine

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This study was undertaken to investigate whether adenosine administered during cardioplegic arrest could enhance myocardial protection and improve recovery of function after ischemia. Isolated perfused rabbit hearts were subjected to 120 minutes of hypothermic (32°C) multidose cardioplegia–induced ischemia. Control hearts ($n = 23$) received modified St. Thomas's cardioplegia, and the remaining hearts received cardioplegia with either 100 μM ($n = 11$), 200 μM ($n = 11$), or 400 μM ($n = 11$) adenosine. After ischemia and 45 minutes of reperfusion, left ventricular contractility was superior in all groups of adenosine-treated hearts compared with control hearts. Furthermore, there was a significant incremental increase in functional recovery with increasing dose of adenosine. Postischemic diastolic stiffness was significantly better in all adenosine groups compared with controls. No differences were noted in coronary flow or myocardial water content between adenosine-treated and control hearts. These data demonstrate that adenosine administered in these concentrations provides myocardial protection and improved recovery of both systolic and diastolic function after global ischemia, presumably metabolically by reducing depletion of adenosine triphosphate or enhancing repletion of adenosine triphosphate and enabling improved postischemic recovery.

(Ann Thorac Surg 1989;47:809–15)

To provide myocardial protection during aortic cross-clamping, multidose potassium cardioplegia and deep myocardial hypothermia have become widely accepted clinical techniques. Even with these protective techniques, however, marked adenosine triphosphate (ATP) depletion can occur during ischemia.

Because intracellular ATP is essential for myocardial contraction and relaxation, depletion of ATP could be a key factor contributing to the incomplete recovery of ventricular function after ischemia and reperfusion. The slow restoration of ATP after ischemia may not be caused by an inability to rephosphorylate precursors, but rather by a reduced availability of precursors, such as adenosine.

Accordingly, this study tested the hypothesis that functional recovery is limited by a lack of adenosine and that increased availability of exogenous adenosine would lead to improved functional recovery after global ischemia.

Material and Methods

Studies were performed in 56 isolated, perfused rabbit hearts. Male New Zealand White rabbits weighing 3 to 4 kg were anesthetized with intravenously administered sodium pentobarbital (10 mg/kg), after which the heart was removed through a median sternotomy. The beating heart was immediately immersed in cold (4°C) Krebs-Ringer bicarbonate solution, after which it was suspended from a perfusion column by aortic cannulation within 30 seconds of excision. Coronary perfusion was established at 80 mm Hg, and the perfusate used was a modified, oxygenated Krebs-Ringer bicarbonate solution (pH 7.44 to 7.48, 300 to 310 mosm/L). The oxygen tension of the perfusate was maintained between 450 and 550 mm Hg, and the perfusate temperature was kept at 37°C by means of a heat exchanger in the perfusion column (Fig 1). The perfusion solution was passed through a No. 40 polyester filter to remove particulate matter, and was not recirculated.

After coronary perfusion was initiated, the heart generally regained sinus rhythm, but in the presence of persistent fibrillation, immediate direct-current cardioversion was carried out. While the heart was perfused on the column, a portion of the mitral valve with its chordae was excised, and a latex balloon, connected to tubing filled with saline solution, was introduced into the left ventricle through the mitral orifice (Fig 2). The balloon was sewn in place in such a way as to allow passive venting of the left ventricular (LV) cavity. The balloon was connected through the saline solution–filled tubing to a Statham P23Db pressure transducer, and LV pressure was recorded continuously. Output from the pressure transducer was electronically differentiated with a Statham amplifier to enable continuous recording of the rate of rise of LV pressure (dP/dt). Left ventricular pressure and dP/dt were recorded on a Gould pressurized ink chart recorder (model 26005).

All hearts had a rate of 120 to 130 beats per minute. During the control period before ischemia, a volume of saline solution was introduced into the LV balloon to produce an end-diastolic pressure (EDP) of 10 mm Hg. The same volume was used to evaluate ventricular systolic performance during reperfusion. By increasing LV volume in increments, diastolic stiffness was estimated before and after the interval of ischemia by measuring the

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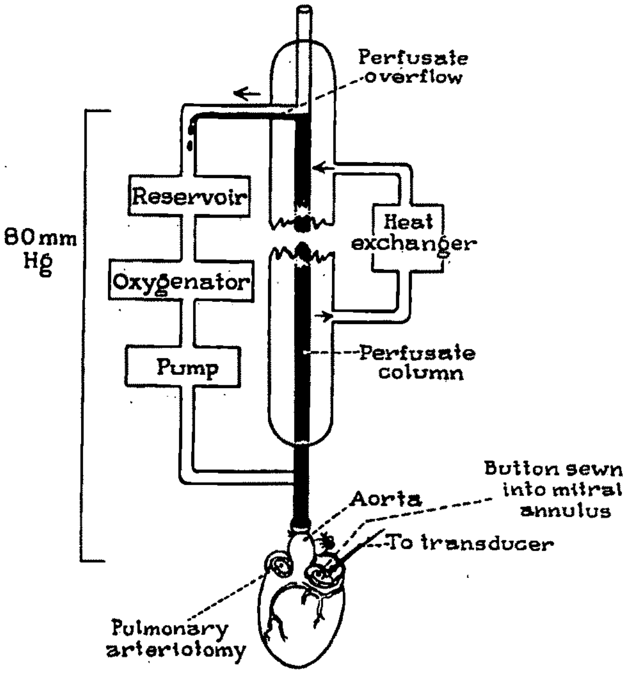


Fig 1. Perfusion column for isolated heart preparation.

slope of linearized EDP versus end-diastolic volume curves for each heart. Coronary flow was measured volumetrically. A thermistor needle was inserted into the midmyocardium to record myocardial temperature.

After a 30-minute stabilization period, control measurements of EDP, developed pressure (DP; peak systolic pressure − EDP), peak positive dP/dt, coronary flow, and diastolic stiffness were made in each heart. Hearts were then rendered globally ischemic by interruption of the perfusion column immediately above the aortic cannulation site. The intraventricular balloon was deflated, and 15 mL of cardioplegic solution was administered.

All hearts were maintained at 32°C by means of a circulating water jacket during 120 minutes of total ischemia. All hearts received 10 mL of cardioplegic solution every 30 minutes during ischemia. Control hearts (n = 23) received modified St. Thomas's cardioplegia, and experimental hearts (n = 11 in each group) received modified St. Thomas's cardioplegia with the addition of 100 μM, 200 μM, or 400 μM adenosine.

Reperfusion was performed with the perfusate temperature at 37°C and delivered with 80 mm Hg pressure for all hearts in all groups. Defibrillation was performed as needed during the initial three minutes of reperfusion. The rate of spontaneous defibrillation and the need for and number of electrical defibrillations were recorded for all hearts. During the initial 15 minutes of reperfusion, the intraventricular balloon was kept deflated to simulate the beating, nonworking condition. After the initial 15 minutes of reperfusion, the LV balloon was refilled to the preischemic control volume and measurements of EDP, DP, dP/dt, diastolic stiffness, and coronary flow were made. The balloon remained inflated for the remainder of reperfusion. Measurements of LV function were obtained after 15, 30, and 45 minutes of reperfusion. Creatine kinase loss from coronary sinus effluent was also measured (Sigma Diagnostics, St. Louis, MO) at these intervals.

After 45 minutes of reperfusion, all hearts were removed from the perfusion apparatus. The myocardial water content was determined by weighing a fresh specimen of myocardium, allowing this sample to desiccate for 48 hours at 80°C, and then reweighing the sample. Percent water was calculated using the formula ([1 − dry weight/wet weight] × 100 − %H_2O).

Statistical analysis was performed with Student's two-tailed *t* test, and a *p* value of less than 0.05 was considered significant. All results are expressed as the mean ± the standard error of the mean.

Results

Left Ventricular Function

There were no significant differences in the prearrest DP or dP/dt values between control hearts and those receiving adenosine for any group. Preischemic DP for all hearts was 111 ± 4 mm Hg. Left ventricular systolic and diastolic functional measurements of DP ± dP/dt were made after 15, 30, and 45 minutes of reperfusion, and were expressed as percent return of function compared with the prearrest isovolumic control values. Left ventricular EDP was also measured in 15-minute intervals after reperfusion and

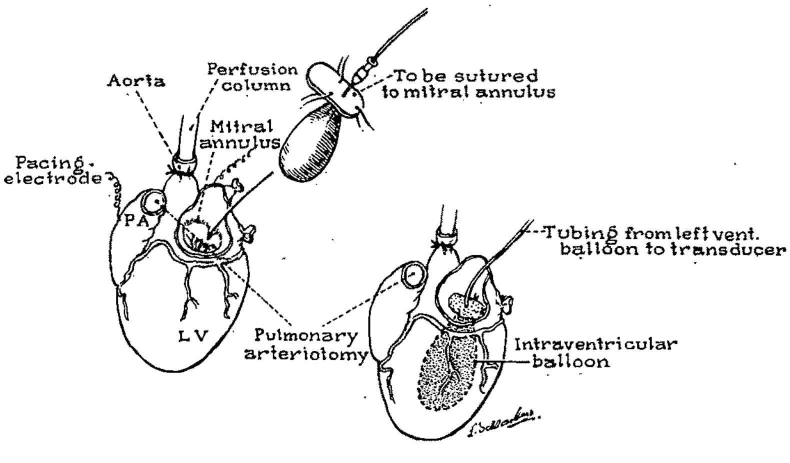


Fig 2. Balloon inserted into left ventricular cavity for recording functional measurements. (LV = *left ventricle;* PA = *pulmonary artery.)*

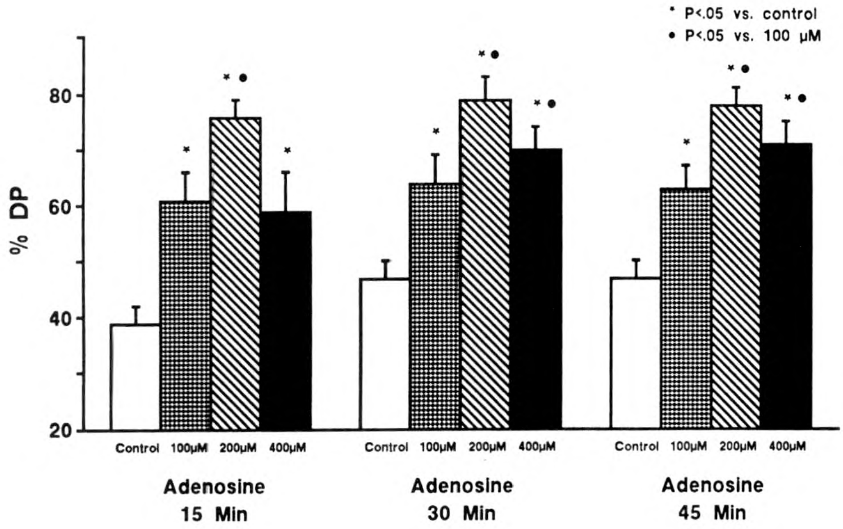


Fig 3. Recovery of developed pressure with time of reperfusion. (% DP = percent of developed pressure compared with preischemic baseline level.)

was expressed as increase in EDP over the preischemic control EDP value of 10 mm Hg. Diastolic stiffness, measured by the slope of linearized EDP versus end-diastolic volume curves, was assessed for each heart at 15-minute intervals after reperfusion, and was expressed as raw data.

After 120 minutes of hypothermic ischemia and 45 minutes of reperfusion, control hearts recovered 47.1% ± 3.3% of the preischemic DP and 47.0% ± 4.1% of preischemic dP/dt. There was significantly better recovery of LV function in the hearts treated with 100 μM adenosine (Fig 3) with 62.5% ± 4.0% recovery of DP and 62.9% ± 6.7% recovery of preischemic dP/dt ($p < 0.05$ versus control hearts). Both the hearts treated with 200 μM and 400 μM adenosine had significantly better recovery of function than either the control hearts or the hearts treated with 100 μM adenosine. Hearts treated with 200 μM adenosine recovered 77.8% ± 3.3% of preischemic DP and 75.0% ± 6.5% of preischemic dP/dt, whereas hearts treated with 400 μM adenosine recovered 70.2% ± 3.7% of preischemic DP and 76.0% ± 2.8% of preischemic dP/dt ($p < 0.05$ versus both control hearts and hearts treated with 100 μM adenosine, but p = not significant versus each other).

Left ventricular EDP, though only an estimate of diastolic function in this model, was significantly lower at all times during reperfusion in the hearts treated with 200 and 400 μM adenosine compared with control hearts and hearts treated with 100 μM adenosine (Fig 4). After 45 minutes of reperfusion, control hearts demonstrated elevated LVEDPs, with a 30 ± 5 mm Hg rise in LVEDP, whereas the hearts treated with 100 μM adenosine had a 28 ± 3 mm Hg elevation in LVEDP. However, the hearts treated with 200 μM adenosine showed only a 10 ± 3 mm Hg rise in LVEDP and the hearts treated with 400 μM adenosine, only a 14 ± 3 mm Hg rise.

The slope of linearized EDP versus end-diastolic volume curves was determined for each heart in the prearrest period as well as during reperfusion. Duplicate curves were obtained, which showed no significant changes that could be attributed to stress relaxation. An example of individual stiffness curves for a control heart and a heart treated with 200 μM adenosine is seen in Figure 5.

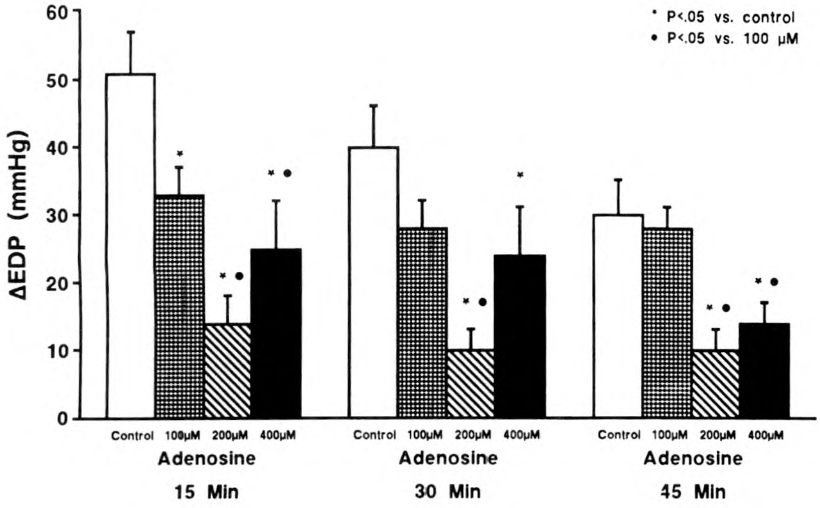


Fig 4. Change in end-diastolic pressure (ΔEDP) with time of reperfusion.

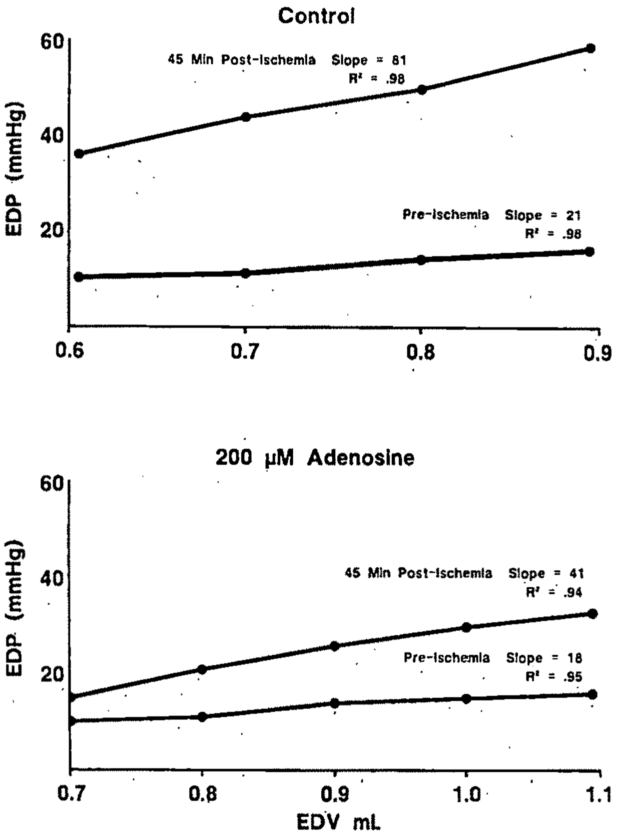


Fig 5. Individual examples of generated end-diastolic pressure (EDP) versus end-diastolic volume (EDV) curves before and after ischemia for a control heart and a heart treated with 200 µM adenosine.

Diastolic stiffness in the adenosine-treated hearts was significantly lower at all times during reperfusion compared with untreated hearts (Fig 6). After 45 minutes of reperfusion, the control hearts were characterized by a diastolic stiffness slope value of 65 ± 3 (a 6.5 ± 0.3 mm Hg rise in EDP for each 0.1-mL increase in end-diastolic volume) versus a diastolic stiffness value of 45 ± 2 in the hearts treated with 100 µM adenosine ($p < 0.05$). The 200 and 400 µM adenosine groups were not significantly different from one another in terms of diastolic stiffness (31 ± 3 and 32 ± 5, respectively; $p < 0.05$ compared with control and 100 µM adenosine groups).

Coronary Flow and Myocardial Water Content

Coronary flow during reperfusion demonstrated no differences between control and adenosine-treated hearts in any group at any time during reperfusion. Prearrest values were also similar in all of the groups. After 45 minutes of reperfusion, coronary flow was 39 ± 3 mL/min in the control group and 39 ± 2, 45 ± 3, and 42 ± 4 mL/min (p = not significant) in the 100 µM, 200 µM, and 400 µM adenosine groups, respectively.

The myocardial water content after 45 minutes of reperfusion was 84% ± 3% for control hearts and 86% ± 9% for hearts treated with 100 µM adenosine. In the 200 µM and 400 µM adenosine groups, the myocardial water content was 84% ± 2% and 85% ± 3%, respectively. There were no significant differences between any of these results.

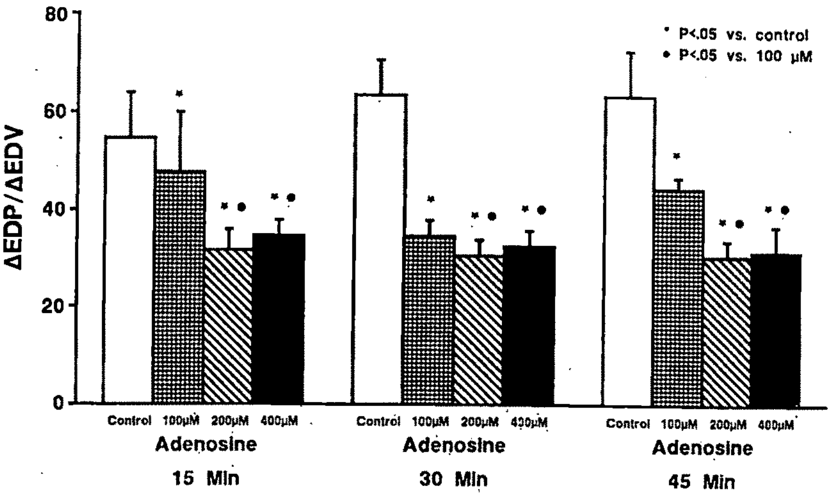
Creatine Kinase Release

Creatine kinase loss from the coronary sinus measured after reperfusion was no different in any of the groups. There was a loss in the control hearts of 296 ± 28 IU/L as opposed to 256 ± 19 IU/L in the 400 µM adenosine group. Although these two measurements are not significantly different, the maximum period of creatine kinase loss may be during the initial few minutes of reperfusion, and measurements were not made at this time.

Ventricular Arrhythmias

The onset of electrical activity after reperfusion was monitored closely in all groups. Of the adenosine-treated hearts, 100% (33/33) defibrillated spontaneously with rapid reinstitution of a normal atrial rhythm with an appropriate rate. In contrast 4 (17%) of 23 control hearts required direct-current cardioversion before regaining a normal rhythm. No hearts in either group appeared to have bradydysrhythmias or depression of the conduction system.

Fig 6. Change in slope of end-diastolic pressure (ΔEDP) versus end-diastolic volume (ΔEDP) curves with time.



Comment

These results demonstrate significant improvement in myocardial functional recovery with the administration of adenosine during ischemia. The mechanism of this improvement may be metabolic, based on increasing available adenosine, a precursor of ATP.

Many investigators [1–4] have shown that myocardial high-energy phosphate levels and adenosine levels decrease during ischemia. Because high-energy phosphate compounds are essential for myocardial contraction and relaxation, as well as maintenance of cellular integrity, any reduction in high-energy phosphate compounds may have severe effects on myocardial cells. Reduction in myocardial ATP content has been shown to be proportional to the incomplete recovery of ventricular function seen after ischemia [5].

The decrease in adenine nucleotides after ischemia can be reversed by two major pathways. The first pathway is by synthesis and regeneration of the nucleotide pool. However, this pathway is extremely slow; only 0.4% of the total nucleotide pool is resynthesized per hour. It can be calculated that if ATP levels were reduced to one half of their preischemic level, it would take up to 1 week for complete restoration of ATP through the new synthesis pathway [6].

The second pathway, which is far more efficient, is the salvage pathway. This pathway involves rephosphorylation of adenosine by the enzyme adenosine kinase to adenosine monophosphate, where it would be available for regeneration to ATP. This salvage pathway can function effectively only if adenosine is available for phosphorylation. Although this salvage pathway involving rephosphorylation of adenosine is quite efficient and rapid, it depends on the availability of intracellular adenosine as a precursor. If there is a washout of adenosine from the extracellular space after ischemia, then these nucleotide precursors are not available for the salvage pathway. Many investigators [5, 7–10] have suggested that the prolonged period required for the repletion of ATP levels is not due to an inability of the mitochondria to rephosphorylate precursors but rather to an inadequate availability of adenosine for the salvage pathway itself, caused by the washout of adenosine.

Isolated mature cardiac myocytes have been used to establish the kinetics of uptake and salvage of adenosine and its breakdown product inosine [11]. This was accomplished by measuring the distribution of radioactive nucleotides incorporated into ATP, adenosine diphosphate, and adenosine monophosphate. When the maximum rates of catalysis of these reactions of the salvage pathway were calculated, it was established that mature myocytes have little capacity to salvage inosine. Adenosine is the favored substrate for the salvage pathway. Furthermore, enzyme measurements indicate that the rate of adenosine salvage of intracellular adenosine would be eight times the rate exhibited by intact myocytes dependent on extracellular adenosine as substrate. These data indicated that the rate of transport of adenosine across myocyte cell walls is the limiting step in the salvage of adenosine from extracellular sources. Therefore, intracellular adenosine is the best substrate for high-energy phosphate regeneration, and the ideal situation may involve maintaining high intracellular concentrations of adenosine during ischemia by either increasing the total amount of adenosine or not allowing adenosine to leave myocytes during ischemia.

Studies on mature rat cardiac myocytes demonstrate that adenosine influx occurs through a saturable transport system with a Michaelis-Menten constant (K_m) of 6.2 μM and a maximum velocity of 0.96 pmol/mg/s [12]. Adenosine transported into cells through the system is rapidly phosphorylated to adenosine monophosphate, and at extracellular adenosine concentrations of less than 32 μM, there is little increase in intracellular adenosine concentration (at this rate of transport, adenosine is immediately phosphorylated to adenosine monophosphate as soon as it enters the cell). However, at concentrations greater than 32 μM, intracellular adenosine accumulates. At adenosine concentrations of greater than 100 μM, there is evidence of a nonsaturable component of adenosine transport into myocytes. Adenosine enters myocytes by mass action. This concentration of adenosine was chosen as the lowest dose in the study and was progressively doubled in an attempt to increase intracellular myocyte adenosine concentration during ischemia and therefore have the highest quantity of purine nucleotide precursors in myocardial cells available for the salvage pathway when reperfusion occurred.

Other studies have shown a favorable effect of adenosine on the recovery of ventricular function after ischemia in many different models. Investigators [1] have demonstrated in the isolated, isovolumetrically contracting rat heart preparation that the addition of adenosine at the 100-μM level during ten minutes of global normothermic ischemia enhanced the recovery of ventricular function and the repletion of ATP levels. In this experiment, ATP levels measured in freeze-clamp biopsy specimens were significantly higher versus controls at the end of a ten-minute period of ischemia as well as at all times during one hour of 37°C reperfusion. Furthermore, when function was assessed, LVDP in the adenosine-treated group at the end of 30 and 60 minutes of reperfusion was significantly greater than in the untreated groups (96% ± 3% and 95% ± 3% versus 73% ± 6% and 73% ± 6%, respectively). These results suggest that in this model, 100 μM adenosine enhanced myocardial preservation and functional recovery perhaps by reducing the net degradation of ATP during ischemia or by facilitating the repletion of ATP during reperfusion.

Other authors [2] have demonstrated in an isolated, working rat heart preparation that the addition of 20 μM adenosine or 80 μM EHNA (erythro-9,2-hydroxy-3-nonyl adenine hydrochloride, an adenosine deaminase inhibitor) was able to prevent a drop in myocyte adenosine levels during 30 minutes of ischemia. Although EHNA alone was not sufficient to demonstrate improved ventricular recovery, when both EHNA and adenosine were used together, presumably preventing adenosine loss from myocytes during ischemia, myocardial tissue ATP levels were maintained at greater than 1 μM/g, which was associated with markedly improved functional recovery during the reperfusion period. These findings are consistent with those of others [3,13], who also demonstrated that adenosine was effective in maintaining tissue ATP levels and enhancing functional recovery in global-stunning models.

The normal plasma adenosine level is 0.1 to 0.3 μM [14]. When adenosine is administered at concentrations higher than this, it has many physiological myocardial and systemic effects. The most pronounced of these is vasodilation. It has been shown that a doubling of adenosine levels from 0.25 to 0.5 μM is associated with a 50% increase in vasodilation [14, 15]. In the model selected for this experiment, a crystalloid-perfused isolated heart, maximum vasodilation probably occurs continuously, perhaps because of low total oxygen delivery. A vasodilator effect of adenosine was not demonstrated at any concentration in this model. Therefore, any favorable action of adenosine did not come from an increase in coronary flow. In fact, coronary flow did not differ at any time in any group versus control. Although intravenous administration of adenosine may have the effect of systemic vasodilation, when administered in the manner of this study (in cardioplegia), adenosine would have very little systemic effect. In a recent study in rabbits [16], an infusion of 4 mg of adenosine per hour per kilogram of body weight was shown to increase the myocardial tissue level of adenine nucleotides by 39% and did not result in systemic hypotension.

Other direct cardiac effects of adenosine include transient negative chromotropic and dromotropic effects, which have been described in many species [10, 17, 18], including humans. There is good evidence that adenosine transiently affects both the sinoatrial and the atrial ventricular nodes in humans, and that these effects are not mediated by vagal mechanisms. In our present study, after reperfusion, the hearts were not paced to allow adequate determination of heart rate and recovery of ventricular rhythm. In this model, no significant differences were noted in heart rate, fibrillation rate, or the need for direct-current cardioversion in the treated groups compared with controls.

Finally, there is evidence that adenosine has a negative inotropic action on myocardial contractility [19], perhaps through an antiadrenergic mechanism. Recent studies have shown that adenosine appears to serve as a negative feedback modulator of β-adrenergic–mediated contractile response in the heart by attenuating the activation of β-receptor–dependent adenylate cyclase activity. Although adenosine may antagonize the positive inotropic effect of many drugs (isoproterenol hydrochloride, histamine phosphate, dopamine hydrochloride), these studies are in isolated papillary muscles, and other studies [20] demonstrate no negative or even a slight positive inotropic effect of adenosine on ventricular preparations.

This present study demonstrated an increase in functional recovery after an ischemic injury with increasing dosage of adenosine. There appears to be a dose response to adenosine in this model, which plateaus at 200 μM adenosine concentration. However, all levels of adenosine concentration resulted in an increase in ventricular function following ischemia compared with controls. The mechanism of the favorable action of adenosine in this model is presumably due to the increased availability of intracellular adenosine on reperfusion, which allows regeneration of ATP, leading to better functional recovery. The mechanism by which adenosine achieved this, when administered exogenously, may be by mass effect, forcing adenosine into cells along an overwhelming passive diffusion gradient. Other investigators [21] have suggested that in addition to this mechanism, adenosine may block the breakdown of ATP during ischemia, which could lead to higher ATP levels after reflow. These mechanisms warrant further investigation and measurement of high-energy phosphate compounds during ischemia and reflow.

However, regardless of the mechanism of adenosine, it has been shown in this model that adenosine administered exogenously during the time of ischemia can favorably enhance myocardial protection and, therefore, functional recovery after ischemia. Although this is a crystalloid-perfused model and not completely applicable to patient use, adenosine may be a useful clinical tool in cardiac operations, especially those on patients susceptible to myocardial injury during ischemia.

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REVIEW OF RECENT BOOKS

The Heart Surgery Handbook. A Patient's Guide

By C. Cohan, J. B. Pimm, and J. R. Jude
Miami, The Pickering Press, 1988
227 pp, illustrated

Reviewed by Benson B. Roe, MD

This 227-page handbook is a uniquely comprehensive, detailed dissertation covering every imaginable aspect of open heart surgery from the patient's viewpoint. The text is lucid and the lay-reader will rarely encounter a term that is esoteric. The contents are divided into 11 chapters that cover not only each step of the hospital course but also each step in the rehabilitation process, the psychological problems, and the role of friends and relatives. A comprehensive glossary is also provided.

Although the authors' objective is highly commendable and serves a very important purpose, I believe that the sheer volume of material not only is more than most lay-readers are likely to digest but also is more than the subject matter requires, with too many details and too many exemplifying anecdotes. The result is to render an otherwise excellent product into a somewhat tedious chore.

The reading patient is provided with opinions and recommendations that, although not exactly dogmatic, are not necessarily those of the entire practicing specialty. On the other hand, the book has a very desirable impact on the standards of care and management by presenting logical and largely irrefutable rationale for its recommendations.

Certainly the handbook will provide a useful preparation for cardiac surgical patients even if only a few get all the way through it. It should result in some comfort and reassurance.

Surgeons who plan to recommend it for their patients would be well advised to read it themselves to make sure that their own management process does not have gaps that will leave the patient disappointed.

San Francisco, CA

Emergency Coronary Artery Bypass Grafting for Failed Angioplasty: Risk Factors and Outcome

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It has been suggested that coronary artery bypass grafting (CABG) performed in the setting of emergent failure of percutaneous transluminal coronary angioplasty causes minimal increased risk compared with routine CABG. We reviewed the records of 103 patients undergoing emergency CABG for failed percutaneous transluminal coronary angioplasty (group 1) and compared them with an identical number of consecutive CABG patients from 1987 (group 2). Group 1 had a lower risk profile evidenced by lower mean age ($p < 0.01$), fewer diseased vessels ($p < 0.0001$), better ventricular function ($p < 0.001$), fewer left main lesions ($p < 0.0001$), and fewer patients with acute ischemia requiring intravenous administration of nitroglycerin ($p < 0.01$). Despite these differences, the group 1 patients had a higher mortality rate (11% versus 1%; $p < 0.01$) and a higher rate of perioperative infarctions (new Q wave) (22% versus 6%; $p < 0.01$). An analysis of risk factors was performed in the group 1 patients using 36 preoperative and operative variables. Multivariate analysis revealed that left ventricular score ($p < 0.0001$), preoperative (after percutaneous transluminal coronary angioplasty) need for inotropic support ($p < 0.005$), and age ($p < 0.025$) were independent predictors of operative mortality. In conclusion, emergency CABG after failed percutaneous transluminal coronary angioplasty carries a significantly greater risk of operative death and perioperative infarction than elective CABG.

(Ann Thorac Surg 1989;47:816–23)

In the last decade, percutaneous transluminal coronary angioplasty (PTCA) has become widely used. Approximately 100,000 PTCAs were performed in 1985, and this number promises to increase in the future. Approximately 5% of these procedures result in acute ischemic complications necessitating emergency surgical intervention. Controversy exists regarding the risk of coronary artery bypass grafting (CABG) in this setting. To investigate this concern, we reviewed our experience with patients undergoing emergency CABG for failed PTCA. These patients were compared with a control group of consecutive CABG patients who had not undergone angioplasty before CABG. Risk analysis was performed on the patients undergoing CABG for failed PTCA to identify predictors of morbidity and mortality.

Material and Methods

Between May 1983 and December 1987, 2,418 patients underwent PTCA at St. Louis University Medical Center and St. Mary's Health Center. There were 103 patients (4.3%) who underwent emergency CABG for the treatment of acute ischemic complications of PTCA. These patients constitute group 1. The last 103 consecutive patients undergoing CABG in December 1987 constitute group 2.

The medical records of both groups were retrospectively analyzed. Clinical variables recorded included age, sex, and the severity of angina (Canadian Cardiovascular Association classification). Also recorded were the presence of concomitant medical diseases including essential hypertension, peripheral vascular disease (history of claudication, rest pain, or aneurysmal disease), cerebrovascular disease (history of stroke, transient ischemic attack, or prior carotid endarterectomy), renal insufficiency (creatinine level ≥ 2.0 mg/dL), diabetes mellitus treated with either insulin or oral medication, and chronic obstructive pulmonary disease (defined as use of bronchodilators). Pertinent recorded cardiac variables included history of congestive heart failure, history of arrhythmia, and ongoing congestive heart failure (defined as simultaneous use of digoxin and furosemide). The occurrence of a prior myocardial infarction (MI) and the interval between MI and PTCA or CABG were noted. Infarctions were categorized as acute (within seven days before revascularization), recent (eight to 30 days), or remote (>30 days). The requirement for intravenous administration of nitroglycerin, intraaortic balloon (IAB) counterpulsation, or inotropic support before PTCA or CABG was noted. Data gathered at catheterization included the presence of cor-

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onary artery disease (defined as ≥70% luminal occlusion in any plane on coronary angiography), left mainstem disease (≥50% occlusion), left ventricular (LV) end-diastolic pressure, and LV score (as defined by the Coronary Artery Surgery Study [1]).

All patients in group 1 evidenced signs or symptoms of acute ischemia or cardiovascular collapse either in the catheterization laboratory or during the hospitalization for PTCA. Variables recorded after angioplasty failure include the presence or absence of chest pain, ST-T wave changes, cardiac arrest (ventricular fibrillation or asystole), and the requirement for inotropic or IAB support in the catheterization laboratory. The incidence of vascular occlusion, dissection, and perforation was noted as was the occurrence of arrhythmia or unexplained cardiovascular collapse. Operative variables monitored were the number of distal anastomoses performed, the total cross-clamp and cardiopulmonary bypass times, and whether or not an internal mammary artery (IMA) was used as a conduit.

The incidence of operative death (death at any time during hospitalization or within 30 days of operation), perioperative MI (defined as the presence of a new Q wave on the postoperative electrocardiogram [ECG]), and low cardiac output (defined as use of IAB and inotropic support for greater than 24 hours postoperatively) was recorded. Other complications included ventricular arrhythmias necessitating medication, cerebrovascular accident, acute renal failure necessitating dialysis, reoperation for bleeding, and sepsis.

Data were analyzed using the STATVIEW 512 statistical software package (Brainpower, Inc, Calabasas, CA). The two study groups were compared with χ^2 and Fisher's exact tests to determine significant differences for discrete variables. Continuous variables were analyzed using an unpaired two-tailed Student's t test. A p value of less than 0.05 was considered significant.

Risk analysis was performed on group 1 patients. Univariate analysis consisted of a χ^2 or Fisher's exact test for discrete variables and an unpaired two-tailed Student's t test for continuous variables. A p value of less than 0.05 was considered significant, and a p value greater than 0.05 and less than 0.15 was considered marginally significant. All variables that were significant or marginally significant were entered into a stepwise linear regression model for multivariate analysis. Total cardiopulmonary bypass time was deleted from the multivariate analysis because it was more likely to be the result of intraoperative problems than an accurate predictor of complications.

Results

PTCA Failure

The vessel treated and damaged during PTCA was the left anterior descending coronary artery in 61 patients (59%), the right coronary in 28 (27%), the circumflex coronary in 12 (12%), and the left main in 2 (2%). The reasons for failure included arterial dissection and occlusion in 35 patients (34%), occlusion alone in 33 (32%), dissection with decreased flow in 26 (25%), unexplained cardiovascular collapse in 4 (4%), occlusion and perforation in 2 (2%), occlusion and dissection in 2 (2%), and perforation with tamponade in 1 (1%). Signs and symptoms of ischemia included chest pain in 91 patients (88%) and ST-T wave changes in 81 (79%). Twenty-four patients (23%) required inotropic support in the catheterization laboratory and 16 (16%), IAB counterpulsation. Fourteen patients required cardiopulmonary resuscitation or cardioversion, or both, because of ventricular fibrillation or tachycardia.

Ischemic symptoms necessitating CABG occurred in the catheterization laboratory in 90 patients (87%), within the first 24 hours after PTCA in 12 (12%), and in 1 patient (1%) on day 4 when systemic heparinization was discontinued. All patients not in the laboratory were returned there to identify the cause of ischemia before surgical revascularization.

Failed PTCA CABG (Group 1) Versus CABG 1987 (Group 2)

The preoperative profiles of both patient groups are depicted in Table 1. The group 2 patients were older by nearly 5 years on average ($p < 0.01$). There was no difference in the proportion of female patients between the two groups. Angina severity was greater in group 2 as evidenced by the increased requirement for preoperative intravenous administration of nitroglycerin ($p < 0.001$). The groups were similar with respect to the incidence of arrhythmia, congestive heart failure, and prior MI. The interval between infarction and intervention (either CABG or PTCA) was also similar.

There were significant differences in the catheterization variables recorded. The group 1 patients had less severe coronary artery disease as evidenced by a lower incidence of left main occlusive disease ($p < 0.002$) and a lesser number of diseased coronary vessels ($p < 0.0001$). Furthermore, left ventricular function was better in these patients ($p < 0.0001$).

At operation, the group 2 patients had a greater number of distal anastomoses performed than did group 1 ($p < 0.0001$) (Table 2). One quarter of the anastomoses (83/339, 24.5%) in group 2 were constructed using one or more IMA grafts in 55 patients. In none of the group 1 patients was the IMA used ($p < 0.0001$). The mean cross-clamp and cardiopulmonary bypass times were significantly increased in the group 2 patients, probably as a result of the increased number of grafts per patient in this group.

Operative mortality was greater in group 1 (11% versus 1%; $p < 0.01$). Low cardiac output was the cause of death in the 1 group 2 patient who died. Among the group 1 patients who died, 4 could not be weaned from bypass and 4 others died of complications from low cardiac output at one day (3 patients) and 12 days postoperatively. There was 1 death each from bleeding with tamponade (one day), renal failure with sepsis (eight days), and profound hypoxic brain damage (four days).

Perioperative MIs occurred more frequently in group 1, whether measured by new Q waves on the ECG (23 versus 6; $p < 0.005$) or by a rise in the creatine kinase isoenzymes postoperatively (41 versus 14; $p < 0.0001$). The incidence of postoperative low cardiac output in group 1 was nearly twice that of group 2 (22 versus 12),

Table 1. Variables Before Intervention[a]

Variable	Group 1: Failed PTCA (n = 103)	Group 2: CABG 1987 (n = 103)	*p* Value
Clinical			
Age (yr)	59.3 ± 11.0	63.9 ± 10.0	<0.01
Female sex	31	30	NS
Hypertension	51	45	NS
Cerebrovascular disease	7	6	NS
Peripheral vascular disease	7	10	NS
Respiratory insufficiency	2	8	NS
Insulin-dependent diabetes mellitus	2	7	NS
Chronic obstructive pulmonary disease	4	2	NS
Cardiac history			
Angina class (CCA)	3.3 ± 0.9	3.5 ± 0.9	NS
Congestive heart failure	6	10	NS
History of arrhythmia	7	8	NS
History of myocardial infarction			
Acute (<7 days)	7	10	NS
Recent (8–30 days)	14	13	NS
Remote (>30 days)	19	29	NS
Preinfarction treatment			
Intravenous nitroglycerin	6	24	<0.001
Inotropic support	1	1	NS
Intraaortic balloon counterpulsation	2	3	NS
Catheterization			
Left main disease	3	17	<0.002
No. of diseased coronary vessels	1.8 ± 0.7	2.6 ± 0.6	<0.0001
Left ventricular score	6.7 ± 2.5	8.2 ± 2.8	<0.0001

[a] Data are shown as actual patient numbers or the mean ± the standard deviation.

CABG = coronary artery bypass grafting; CCA = Canadian Cardiovascular Association; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

but this difference did not quite achieve significance (p = 0.09). There were no differences in the other recorded complications, which included ventricular arrhythmia, stroke, acute renal failure necessitating dialysis, sepsis, and reoperation for bleeding.

Risk Analysis for CABG After Failed PTCA (Group 1)

The 103 patients undergoing emergency CABG after failed PTCA were assessed to identify risk factors. Thirty-six preoperative and operative variables (Appendix 1) were used in the risk analysis model. Univariate (Table 3) and multivariate (Table 4) analyses were performed to identify significant independent predictors of operative mortality, perioperative MI (new Q wave), and postoperative low cardiac output.

Analysis of operative mortality in group 1 revealed significant differences between survivors and nonsurvivors in regard to preoperative LV function as evidenced by LV score ($p < 0.0001$) and LV end-diastolic pressure ($p < 0.005$) (see Table 3). Other significant univariate predictors of operative mortality were acute MI (within seven days before PTCA) ($p = 0.05$) and the requirement for inotropic support in the catheterization laboratory after failed PTCA ($p < 0.005$). Age was a marginally significant variable ($p = 0.15$). These five variables were then entered into the multivariate analysis (see Table 4). Only LV score ($F = 18.94$, $p < 0.0001$), inotropic support in the catheterization laboratory ($F = 9.92$, $p < 0.005$), and age ($F = 6.65$, $p < 0.025$) were found to be significant independent predictors of mortality.

Both insulin-dependent diabetes mellitus ($p < 0.05$) and preoperative ST-T wave changes on the ECG ($p < 0.05$) were significant univariate predictors of perioperative MI in group 1 (see Table 3). The need for placement of an IAB in the catheterization laboratory was of marginal significance ($p < 0.10$). After multivariate analysis, only insulin-dependent diabetes mellitus ($p < 0.005$) and ST-T wave changes ($p < 0.025$) were found to be significant predictors (see Table 4).

In the univariate analysis, several variables were found to be predictive of postoperative low cardiac output (see Table 3). These included LV score ($p < 0.0001$), LV

Table 2. Perioperative Variables[a]

Variable	Group 1: Failed PTCA (n = 103)	Group 2: CABG 1987 (n = 103)	*p* Value
Operative			
No. of distal anastomoses	2.4 ± 1.1	3.4 ± 1.0	<0.0001
No. of patients with IMA used	0	55	<0.0001
Cross-clamp time (min)	44.9 ± 22.9	70.6 ± 24.8	<0.0001
Cardiopulmonary bypass time (min)	100.9 ± 59.7	125.8 ± 36.9	<0.001
Postoperative			
Death	11	1	<0.01
Perioperative myocardial infarction			
New Q wave on postop ECG	23	6	<0.005
CK-MB rise	41	14	<0.0001
Low cardiac output	22	12	NS
Ventricular arrhythmia	20	15	NS
Stroke	3	2	NS
Acute renal failure	2	0	NS
Reoperation for bleeding	6	2	NS
Sepsis	6	5	NS

[a] Data are shown as actual patient numbers or the mean ± the standard deviation.

CABG = coronary artery bypass grafting; CK-MB = myocardial-specific isoenzyme of creatine kinase; ECG = electrocardiogram; IMA = internal mammary artery; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

end-diastolic pressure ($p < 0.001$), acute MI (within seven days of revascularization) ($p < 0.05$), preoperative cardiac arrest ($p < 0.0001$), and the institution of inotropic support ($p < 0.0001$) or IAB counterpulsation ($p < 0.0001$) in the catheterization laboratory. Factors of marginal significance included the number of diseased coronary arteries ($p < 0.10$), female sex ($p < 0.15$), and the occurrence of chest pain in the catheterization laboratory after failed PTCA ($p < 0.15$). Multivariate analysis yielded only four significant variables: IAB placement ($p < 0.005$) or inotropic support ($p < 0.025$) in the catheterization laboratory, female sex ($p < 0.025$), and LV function ($p < 0.025$) (see Table 4).

Comment

Over the last decade, PTCA has evolved from an investigative technique to a common therapeutic intervention practiced daily in academic and community hospitals alike. Although several pleas have been made for prospective randomized trials comparing PTCA with other therapeutic techniques, there continues to be a paucity of such data to support its widespread use in lieu of CABG [2, 3]. Notwithstanding, balloon angioplasty has been shown to be effective in dilating stenotic vessels and relieving angina and myocardial ischemia. It has also been heralded as a less morbid and more cost-effective alternative to CABG. In addition, many patients and medical personnel believe that PTCA offers a "no-lose" situation; failure of balloon angioplasty simply means the patient must undergo the same low-risk surgical procedure—CABG—he or she would have faced before the inception of PTCA. Our data contradict this notion and demonstrate that patients undergoing emergency CABG for ischemia after a failed PTCA have a markedly increased mortality and morbidity.

Early reports suggested that urgent CABG after failed PTCA could be undertaken with little or no added mortality; however, these series were reported when PTCA was employed in a highly select patient population [4–7]. Virtually all patients had unimpaired ventricles, and the vast majority had a discrete lesion in a single coronary artery. In the initial report from the National Heart, Lung, and Blood Institute PTCA Registry [8], the mean patient age was 52 years, 93% of patients had normal ventricles, and 4 out of 5 had single-vessel disease. Such patients are relatively low-risk CABG patients even in the face of PTCA failure. In our own experience, only 1 death occurred among the first 35 patients with single-vessel disease who required emergency CABG after failed PTCA.

However, as PTCA has evolved into accepted therapy for coronary artery disease, the selection criteria for angioplasty have broadened substantially. Elderly patients and those with impaired ventricles are now undergoing PTCA. Multivessel disease, once a relative contraindication to PTCA, is frequently treated by angioplasty even when 100% revascularization cannot be effected. Indeed, in those patients having emergency CABG for failed PTCA, multivessel disease has become the rule rather than the exception at our institution. Only 41% of the patients in whom PTCA failed in this series had single-vessel disease, and since 1985, that proportion has decreased to 33% at our institution. Percutaneous translum-

Table 3. Results of Univariate Analysis of Group 1[a]

Risk Factor	Category	Category	p Value
OPERATIVE MORTALITY	Survivors	Nonsurvivors	
LV score	6.3 ± 2.1	9.9 ± 3.3	0.0001
LV end-diastolic pressure	14.4 ± 7.1	21.8 ± 7.8	0.003
Age (yr)	58.4 ± 10.8	63.8 ± 12.5	0.15
Dopamine infusion after PTCA	17/92 (19)	7/11 (64)	0.003
Acute MI	5/92 (5)	3/11 (27)	0.050
PERIOPERATIVE MYOCARDIAL INFARCTION	None	Present	
ECG changes after PTCA	53/74 (72)	25/26 (96)	0.020
Insulin-dependent diabetes mellitus	0/74 (0)	3/26 (12)	0.021
IAB support after PTCA	8/74 (11)	7/26 (27)	0.097
LOW CARDIAC OUTPUT	Absent	Present	
LV score	6.2 ± 2.0	8.7 ± 3.6	0.0001
LV end-diastolic pressure	13.9 ± 6.6	20.4 ± 8.6	0.0006
No. of diseased coronary arteries	1.7 ± 0.7	2.0 ± 0.6	0.089
Dopamine infusion after PTCA	11/80 (14)	13/22 (59)	0.0001
IAB support after PTCA	6/80 (8)	10/22 (46)	0.0001
Arrest after PTCA	5/80 (6)	9/22 (41)	0.0001
Acute MI	7/80 (9)	7/22 (32)	0.015
Chest pain after PTCA	68/80 (85)	22/22 (100)	0.119
Female sex	21/80 (26)	10/22 (46)	0.141

[a] Numbers in parentheses are percentages.

ECG = electrocardiographic; IAB = intraaortic balloon; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

inal coronary angioplasty is now also used in cases of unstable angina and after thrombolysis in the acute postinfarction period. This broadening of selection criteria has resulted in a group of PTCA candidates who have a relatively higher risk than those of the early 1980s. These patients, however, would still qualify as low-risk candidates for elective CABG.

Multivariate risk analysis for CABG has demonstrated that emergency operation, poor LV function, advanced age, left main occlusive disease, and incomplete revascularization are significant independent predictors of operative mortality [9, 10]. Despite the changing profile of angioplasty candidates, most patients undergoing PTCA still have few or none of these risk factors. Percutaneous transluminal coronary angioplasties are generally elective procedures undertaken in younger patients with less severe coronary disease and better ventricular function than their CABG counterparts [11]. This is confirmed in the present series.

Despite the low-risk status of patients before PTCA, the acute ischemic insult after failure of the angioplasty procedure suddenly reverses those factors that portend a favorable outcome. These patients are transformed into candidates for emergency revascularization with an attendant increase in operative risk. Coronary occlusion results in acute ischemia, which frequently produces LV dysfunction, yet another risk factor. This LV dysfunction was

Table 4. Results of Multivariate Analysis of Group 1

Risk Factor	F Value	p Value
Operative mortality		
LV score	18.94	<0.0001
Dopamine infusion after PTCA	9.92	<0.005
Age	6.65	<0.025
LV end-diastolic pressure	3.46	NS
Acute MI	0.02	NS
Perioperative MI		
Insulin-dependent diabetes mellitus	8.47	<0.005
ECG changes after PTCA	6.14	<0.025
IAB support after PTCA	2.21	NS
Low cardiac output		
IAB support after PTCA	11.29	<0.005
Dopamine infusion after PTCA	6.07	<0.025
Female sex	6.07	<0.025
LV score	5.38	<0.025
No. of diseased coronary arteries	2.02	NS
Chest pain after PTCA	0.87	NS
LV end-diastolic volume	0.51	NS
Acute MI (<7 days)	0.06	NS

ECG = electrocardiographic; IAB = intraaortic balloon; LV = left ventricular; MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

severe enough to necessitate preoperative inotropic and IAB support in one quarter of our patients, an incidence similar to that found by others [12, 13]. The IMA was not used for coronary grafting in this series because of the acute nature of the myocardial ischemia and the additional time necessary for harvesting. Most, if not all, of the patients who had failure of PTCA would have had an IMA used in an elective setting. These patients have been denied the long-term benefits of IMA grafting. Recently, however, we have used reperfusion catheters successfully in 2 patients who were converted to nonischemic status, thus allowing for the takedown and utilization of IMA grafts.

The 11% operative mortality in our report would not have been predicted from the pre-PTCA risk factors, but this figure is essentially identical to those figures in the reports by Page and associates [14], Parsonnet and colleagues [15], and Killen and co-workers [12]. Multivariate analysis suggests that poor LV function, hemodynamic instability necessitating inotropic support, and advanced age, all well-recognized risk factors in elective CABG, appear to maintain their influence on outcome in the emergency setting. The need for inotropic support after PTCA failure was a strong negative predictor, which was associated with a 29% mortality (7/24) in our series.

Yet another factor that may increase the risk is the increasingly aggressive attitude of the interventional cardiologist. At many institutions, the cardiologists are now attempting to treat the ischemic complications of failed PTCA. Thrombolytic agents and repeat dilation are used to reopen occluded vessels. Balloons are also used to "remodel" dissected intimal flaps to prevent thrombosis and occlusion. Recently, implantable stents have been used to maintain coronary patency. In many patients such measures are effective and operation is avoided, at least on a short-term basis. However, those patients in whom these measures fail are subjected to additional minutes or hours of low or intermittent myocardial and systemic perfusion with its attendant ischemic impairment. Such impairment undoubtedly increases the risk of immediate surgical revascularization. If these patients survive CABG, they do experience a much higher incidence of permanent myocardial damage.

Transmural infarctions occurred in 22% of the patients in group 1, an experience similar to that of most investigators. The fact that electrocardiographic changes and the institution of IAB counterpulsation in the catheterization laboratory correlate with perioperative MI has been noted before and is not surprising. However, the association between insulin-dependent diabetes and postoperative infarction is new. This may be due to the diffuse nature of the atherosclerotic process in these patients, which precludes "complete" revascularization without extensive endarterectomies. However, the importance of this factor must await confirmation by other studies.

Postoperative low cardiac output is a common complication after CABG for failed PTCA and is the most common cause of death in most series. Our finding that postoperative low cardiac output correlates with preoperative LV function and the requirement for inotropic or IAB support is not unexpected from the data accumulated regarding elective CABG risks. The correlation of female sex with low cardiac output appears to be a new finding of this study. This also must await confirmation by other investigators.

In summary, the optimal role for PTCA in the treatment of coronary artery disease has not yet been determined despite its widespread use. Although PTCA has proved to be effective in the treatment of ischemic heart disease, much has yet to be learned regarding its indications, durability, and overall economic cost. The treatment of coronary atherosclerosis will likely involve both PTCA and CABG in a complementary rather than competitive fashion. It is hoped that prospective investigations such as the Bypass Angioplasty Revascularization Investigation conducted by the National Heart, Lung, and Blood Institute will be able to shed light on the appropriate utilization of PTCA. For the foreseeable future, PTCA will continue to be used extensively, and it must be understood by physicians and patients alike that it is not a no-risk undertaking. Although success is likely in the majority of patients, a certain percentage of patients will sustain ischemic complications necessitating emergency surgical intervention. The operative mortality and the incidence of permanent myocardial damage are significantly greater for patients having CABG after failed PTCA than for patients undergoing elective CABG.

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Appendix 1

Risk Analysis Variables

- Age
- Sex
- Date of operation
- Medical diseases
  - Hypertension
  - Cerebrovascular disease
  - Peripheral vascular disease
  - Diabetes
    - Insulin dependent
    - Oral medication
  - Chronic lung disease
- Cardiac history
  - Angina severity
  - History of congestive heart failure
  - Congestive heart failure at present
  - History of arrhythmia
  - History of myocardial infarction
    - Acute (<7 days)
    - Recent (8–30 days)
    - Remote (>30 days)
- Catheterization
  - No. of diseased vessels
  - Left main disease
  - Left ventricular score
  - Left ventricular end-diastolic pressure
- Treatment before dilation
  - Intravenous nitroglycerin
  - Inotropic drug support
  - Intraaortic balloon support
- Events after dilation
  - Vessel dilated
  - Chest pain
  - Electrocardiographic changes
  - Cardiac arrest
  - Intubation
- Reason for failure
  - Dissection
  - Occlusion
  - Perforation
  - Unexplained collapse
- Operative variables
  - Interval from PTCA to CABG
  - No. of distal anastomoses
  - Cross-clamp time
  - Cardiopulmonary bypass time

DISCUSSION

DR WILLIAM A. REED (Kansas City, MO): I thank Dr Naunheim and his associates for the opportunity to review their manuscript. They are to be congratulated on a fine presentation as well as for providing additional well-documented evidence that angioplasty may be associated with increased morbidity and mortality compared with elective operation in similar patients. Our experience with failed angioplasty in terms of operative mortality, MI, postoperative bleeding, and problems with cardiac output mirrors their results. The majority of patients done later in their series had multivessel disease. Again this is similar to our experience, and, like that of Naunheim and co-workers, our operative mortality was very low in patients with single-vessel disease, 1 patient of 75 patients.

One group of patients not mentioned by Naunheim and associates comprised 16% of our original series. This group was patients who had had prior CABG. There was a high morbidity and mortality in this group, and all such patients may present an almost insurmountable challenge to the cardiac surgeon. A similar group is patients with intractable cardiac arrest.

Since 1980, approximately 11,615 patients have undergone angioplasty in our institution. Approximately 735 have had CABG after one or more angioplasties. Emergency CABG was necessary in 2.5% of 8,000 patients undergoing PTCA over the last 4 years, and an increasing percentage have had more diffuse disease and prior CABG.

I have a couple of comments to make based on our experience. The use of a bail-out catheter in more recent years has lessened the urgency of operation and possibly reduced acute myocardial injury and mortality. Utilization of IMA grafts in the emergency setting can be safely done in select patients. Last, some dying patients need not complete the process in the operating room; nonoperative management or deferred management may be more appropriate. Some will get better with good medical management and be converted to a lower-risk category, and the refusal of operation in certain circumstances may help the cardiologist review his or her own indications.

I would appreciate a comment from Dr Naunheim regarding his opinion on use of the IMA in the emergency setting, as the IMA was used in none of the patients in this series. I think this points out the compromise of operation in an emergency setting. Second, would he comment on his experience with previous CABG patients, those who have had operations previously, and patient selection, as this can adversely affect or markedly affect the reports in the literature regarding morbidity and mortality?

DR WADE L. KNIGHT (Temple, TX): I have just one question for Dr Naunheim. Did your series include any dire emergencies? By this I mean patients going from the catheterization laboratory to the operating room with cardiopulmonary resuscitation in progress and requiring the initiation of femorofemoral bypass while cardiopulmonary resuscitation was in progress.

DR NAUNHEIM: I thank Dr Reed for his kind comments. At St. Louis University, we have also noted a change in the profile of the angioplasty patients. Those patients who come emergently to the operating room have more complex cardiac disease than the patients we performed emergency bypass on early in the angioplasty experience. As little as 2 to 3 years ago, this type of emergency procedure carried a lesser risk. Usually the patient had single-vessel disease, was young, and had a nearly normal heart. Surgical treatment entailed only a single saphenous vein graft, and often the procedure could be accomplished in a two-hour to three-hour period. At present, this quick and simple procedure happens very rarely after angioplasty failure. In our institution, fewer than one third of the patients come from the catheterization laboratory requiring only a single graft. The vast majority of patients now have multivessel disease and some element of LV impairment. A substantial number of them are septuagenarians, a subset of patients with an already elevated operative morbidity and mortality.

We, like Dr Reed, have begun attempting to use the IMA after failed angioplasty. We believe this is safe if the condition of the patient can be stabilized with the use of a bail-out catheter or an implanted stent. If the patient reverts to a state in which there is no angina and there are no ongoing electrocardiographic changes consistent with ischemia, we think that it is safe to spend the additional time necessary to take down the IMA.

We have also been getting a substantial number of patients who have had previous CABG procedures and have required emergency revascularization. Most often, these patients are placed urgently on femoral bypass to unload the heart while the chest is being opened in as expeditious a fashion as possible.

Last, Dr Reed raised the issue of whether we had turned down any patient for urgent revascularization in this setting. Indeed, we have refused to operate when the patient was 80 years old or more and in cardiogenic shock. In our early experience we found that the mortality rate for such patients was prohibitive, and we believe operation should not be undertaken on this patient subset.

Finally, the question was asked whether or not we have taken any patient from the catheterization laboratory while cardiopulmonary resuscitation was being performed. Several of the patients in the present study could not be resuscitated in the catheterization laboratory and were undergoing cardiopulmonary resuscitation during transport. Three patients were actually placed on femorofemoral bypass and taken to the operating room on partial bypass. Two of these patients died, and 1 is a long-term survivor.

Notice From the Southern Thoracic Surgical Association

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Phoenician Golf and Tennis Resort, Scottsdale, AZ, November 9–11, 1989. There will be a $155 registration fee for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 9, 1989. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1989, to Bradley M. Rodgers, MD, Program Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract submission form. These forms may be obtained from the Association's office. All slides used during the presentation must be 35 mm. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1989 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1989, and forwarded to Hooshang Bolooki, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 111 East Wacker Drive, Chicago, IL 60601.

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Correlates of Survival in Patients With Postinfarction Ventricular Septal Defect

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Prognostic indicators of survival in 42 consecutive patients (21 men and 21 women) with postinfarction ventricular septal defect were reviewed. Infarct location was anterior in 57%, inferior in 33%, and combined in 10%. The hospital mortality among 9 patients not receiving surgical therapy was 100%. Of the 33 surgically treated patients, 19 (58%) survived. Time from diagnosis to operation, ventricular function, and presence or absence of shock were analyzed in a logistic regression model to determine which factors carried independent prognostic value. Shock was independently predictive of operative mortality ($p < 0.01$). Of additional variables examined, nonsurvivors were characterized by a shorter time from postinfarction ventricular septal defect to operation, a relatively higher incidence of inferior infarction, moderate right ventricular dysfunction and mild left ventricular dysfunction, and a lower right ventricular systolic pressure. Results of postmortem examination were available for 15 nonsurvivors. Quantitative analysis of percent ventricle infarcted revealed that in patients with inferior infarctions, a mean of 31% of the right ventricle was infarcted compared with 10% in patients with anterior infarction ($p = 0.059$). Kaplan-Meier survival estimates revealed 1-year survival of 70%, 5-year survival of 55%, and 10-year survival of 20%. Seventy percent of survivors were in New York Heart Association class I or II. These data show that, irrespective of ventricular function or timing of operation, the development of shock is the most important predictor of survival in postinfarction ventricular septal defect. The higher mortality in patients with inferior infarction may be associated with a greater degree of right ventricular infarction and consequent dysfunction. Finally, long-term survival and excellent functional recovery can be achieved in patients undergoing operation.

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Since 1846 when Latham [1] first described postinfarction ventricular septal defect (VSD), it has been recognized as a highly lethal complication of myocardial infarction (MI). Ventricular septal defects (VSDs) occur in approximately 1% of all MIs, but account for up to 2% of deaths subsequent to MI [2]. Previous studies have documented that with nonsurgical therapy, 24% of patients die within the first 24 hours, 60% in the first 2 weeks, and 85% to 90% within 2 months of the appearance of the VSD murmur [3, 4].

Cooley and colleagues [5] reported the first surgical repair in 1957 and with subsequent improvement in operative techniques, surgical correction of postinfarction VSD has become the preferred therapy [6–9]. If operation can be delayed safely, survival rates are enhanced. However, despite intense medical therapy, most patients with postinfarction VSD experience abrupt or rapidly progressive deterioration manifested as cardiogenic shock. Recently, the most successful series indicate that early operation, especially in patients whose condition deteriorates rapidly, is mandatory to alter the otherwise high mortality rate. The clinical factors that appear to have the greatest influence on survival following operation are the presence of shock preoperatively, inferior location of the infarction, and right ventricular (RV) dysfunction [7, 9, 10–14].

The purpose of the present study was to review the clinical outcomes of and identify prognostic indicators in patients with postinfarction VSD treated at Duke Hospital from 1969 through 1986. In particular, the importance of the presence or absence of shock, the timing of operation, and RV impairment as prognostic indicators was investigated.

Material and Methods

The Duke University Cardiovascular Data Bank was used to identify patients with the diagnosis of VSD as a consequence of MI. Medical records were reviewed to determine clinical course and to abstract variables of interest. All surviving patients were subsequently interviewed regarding their present status.

Determination of Left and Right Ventricular Function Angiographically

Results of cardiac catheterizations in 30 patients undergoing surgical intervention were available for review. In each instance, the interventricular septal defect allowed adequate visualization of the right ventricle to assess not only left ventricular (LV) performance but RV performance as well. An experienced angiographer, blinded to the history and outcome of the patient, independently reviewed and analyzed each cineangiogram. The function

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of the right and left ventricles was graded as accurately as possible and rated on a scale of 1 through 4: 1 = normal function; 2 = mild dysfunction; 3 = moderate dysfunction; and 4 = severe dysfunction. This assessment represented a subjective analysis of ventricular dysfunction, as might be done during cardiac catheterization by a surgeon or cardiologist, without the aid of highly specialized techniques, such as segmental wall motion analysis or midcavitary diameter change [7, 10].

Quantitation of Infarct Size

Among the nonsurvivors, there were 15 patients whose original pathology reports and specimens were available for review. To quantitate infarct size, cross sections of the ventricles were made from apex to base, resulting in four to five transverse slices of approximately equal thickness. The basal aspect of each of these slices was photographed. A thin section was taken from the apical surface of each slice to encompass the entire circumference of the ventricles. Tissue was embedded in paraffin, and sections 6 μm thick were stained with Masson's trichrome stain. An average of nine blocks was required to process each of the circumferential slices for microscopic examination. The histological slides were then compared with the photograph of the adjacent basal surface of each subsequent slide. Based on the combined gross and microscopic appearances, the outline of each infarct was drawn on the photograph of the heart slices. In regions where the infarct was patchy, an estimate of the amount of infarcted myocardium was made to the nearest 25%. Subsequently, tracings of the photographs of each heart slice with the outlined boundaries of the infarct were drawn on an x-y digitizer coupled to a DEC-Vax 11-80 for calculation of the percentage of the LV and RV myocardium infarcted [15].

Statistical Analysis

Where appropriate, means or medians of descriptive data were calculated. The variables of shock, LV dysfunction, RV dysfunction, and time until operation were analyzed using a logistic regression model for determination of the factors associated with postoperative in-hospital survival. Survival data were illustrated as a Kaplan-Meier plot. Pathological data were reported as the mean ± the standard deviation. The Wilcoxon-Mann-Whitney nonparametric two-sample test was used to evaluate the relationship of the amount of right and left ventricle infarcted in anterior and inferior infarctions resulting in postinfarction VSD.

Results

Patient Characteristics

From 1969 to 1986, a total of 42 patients with postinfarction VSD were identified. There were 21 men and 21 women. Their mean age was 66 years (range, 50 to 81 years). Review of each patient's electrocardiogram resulted in the diagnosis of anterior infarction in 24 patients (57%), inferior infarction in 14 patients (33%), and combined anterior and inferior infarction in 4 (10%). Twenty-three patients had a history of hypertension for an average of 10 years prior to the postinfarction VSD. There was a history of cigarette smoking in 21 patients, angina in 9 patients, and previous MI in 6 patients. There were no patients with a history of congestive heart failure.

With only one exception, all patients were noted to have a murmur at the time of diagnosis. The diagnosis was documented in 39 patients by demonstration of an oxygen "step-up" from the right atrium to the pulmonary artery. Twenty-six patients had a thrill associated with the murmur, and 23 experienced recurrent chest pain at the time of diagnosis of postinfarction VSD. Of note, 33 patients (79%) were transferred from outside hospitals to our center. Transfer occurred a mean of 12.5 days after the postinfarction VSD.

Therapy for Postinfarction Ventricular Septal Defect

Thirty-three patients received surgical therapy and of them, 19 (58%) were discharged from the hospital. Medical treatment was elected in 9 patients either because deterioration was so rapid that there was no opportunity for surgical intervention, or because patients were transferred to our facility late in the course of the illness when surgical therapy was no longer thought to be appropriate. Among patients receiving medical therapy, mortality was 100% over the 2 months following the postinfarction VSD. In the patients undergoing operation, 19 had anterior infarction, 11 had inferior infarction, and 3 had combined infarctions. Eleven (58%) of the 19 patients with anterior infarctions survived, and 5 (45%) of the 11 patients with inferior infarctions survived. All 3 of the patients with a combined location of infarction survived.

Angiographic Estimation of Left and Right Ventricular Function

For 30 patients, cardiac catheterization data were suitable for study prior to operation. The mean value of LV dysfunction among those patients having operation was 2.6, and the mean value for the right ventricle was 3.2. Thus, of patients having surgical intervention, the right ventricle was thought to have slightly worse dysfunction overall than the left. The grading of LV dysfunction for patients with an anterior location, an inferior location, and a combined location was 2.8, 2.4, and 2.3, respectively. Right ventricular dysfunction was notable in all infarct locations. The mean value was 3.0 for anterior infarctions, 3.4 for inferior infarctions, and 3.0 for combined infarctions. Thus, the right ventricle was moderately to severely affected irrespective of location but was most affected in inferior infarctions. The mean value of LV dysfunction was 3.1 and 2.2 in survivors and nonsurvivors, respectively. However, the mean RV value for survivors and nonsurvivors was similar, 3.2 and 3.1, respectively. Thus, nonsurvivors were characterized by a better subjective grading of LV function compared with survivors while RV dysfunction was similar in both groups.

Shock in Postinfarction Ventricular Septal Defect

All but 5 patients experienced a mean drop in blood pressure of 10 mm Hg when the murmur appeared, and cardiogenic shock developed in 28 patients (67%). Twenty-one (75%) of these 28 patients sustained cardiogenic

Table 1. Effect of Time of Operation and Presence of Shock on Survival

Week After Myocardial Infarction	No. of Patients	No. in Shock	No. Surviving	Survival Rate (%)
1	8	8	2	25
2	6	5	3	50
3	3	2	2	67
4	7	2	5	71
>4	9	2	7	78

Table 2. Clinical Findings in Patients with Postinfarction Ventricular Septal Defect Treated Surgically[a]

Variable	Survivors	Nonsurvivors
No. in shock	8/19 patients	11/14 patients
Time from VSD to operation	Median, 19 days	Median, 3 days
Time from MI to operation	Median, 27 days	Median, 10 days
Anterior location	11/19 patients	8/19 patients
Inferior location	5/11 patients	6/11 patients
Combined location	3/3 patients	0 patients
Right ventricular score	3.2	3.1
Left ventricular score	3.1	2.2
Age (yr)	63	66
Sex	12 M/7 F	6 M/8 F
Hemodynamics		
Systolic blood pressure (mm Hg)	100	84
Heart rate (beats per minute)	96	112
Pulmonary/systemic flow ratio	3.75	3.0
Right ventricular systolic pressure (mm Hg)	57	42
Pulmonary capillary wedge pressure (mm Hg)	21	18
Right atrial pressure (mm Hg)	14	13
Blood urea nitrogen (mg/100 mL)	43	50
Creatinine (mg/100 mL)	2.0	2.5

[a] Unless otherwise noted, data are shown as the mean where applicable.

MI = myocardial infarction; VSD = ventricular septal defect.

shock within three days of the appearance of postinfarction VSD. In the remaining 7 patients, shock developed after varying intervals, in 1 patient on day 67 after the postinfarction VSD. Cardiogenic shock was defined as (1) systolic blood pressure less than 80 mm Hg or mean arterial pressure less than 60 mm Hg, with evidence of end-organ hypoperfusion (obtundation, decreased urine output, elevated levels of creatine or blood urea nitrogen, or cool, clammy skin), or (2) the requirement for mechanical or pharmacological interventions to maintain blood pressure and end-organ perfusion.

Of those patients who underwent operative repair, 58% (19/33) were in cardiogenic shock preoperatively, and 42% of them (8/91) survived. Twelve of the 19 patients with anterior infarctions were in preoperative shock, and 5 (42%) survived. Five of the 11 patients with inferior infarctions were in preoperative shock, and 1 patient (20%) survived. Two of the 3 patients with combined location of infarction were in shock, and both survived. The analysis of shock and patients surviving operation revealed that of the 19 survivors, 8 (42%) were in shock preoperatively whereas of the 14 nonsurvivors, 11 (79%) were in shock preoperatively.

Both the time of operation after MI and the presence or absence of shock appeared to affect survival (Table 1). Patients having operation early after infarction and postinfarction VSD tended to be in shock, and subsequent mortality was high. Notably, of the 2 patients who died who were operated on more than 28 days after infarction, 1 was transferred to our center more than 2 months after the infarction and was in cardiogenic shock with hepatorenal syndrome at the time of transfer. The other patient had refused operation until 2 months after the onset of postinfarction VSD. At the time of surgical intervention, he was experiencing intractable dysrhythmias and hemodynamic instability.

Likewise, of the 2 patients who died who were operated on during week 4 after MI, 1 was transferred to our center nine days after the infarction. This patient was in renal failure, and abdominal distention was noted at the time of admission. The patient died postoperatively of gram-negative sepsis. Autopsy revealed intestinal infarction. The remaining patient, although in stable condition for 3 weeks, sustained shock unresponsive to inotropic or mechanical support, and required emergency operation. This patient died postoperatively of multiorgan failure.

Therefore, for the 16 patients having operation 4 weeks or more after MI, overall survival was 75%. The 4 patients who died experienced shock with end-organ failure of varying degrees preoperatively. The 12 patients who were not in shock survived.

Predictors of Operative Mortality

There were notable differences in several variables assessed between survivors and nonsurvivors in the group of patients undergoing operation (Table 2). Nonsurvivors were characterized by a higher incidence of shock, shorter time intervals between infarction and operation and between diagnosis of postinfarction VSD and operation, and a relatively higher incidence of inferior infarction compared with anterior infarction. In addition, nonsurvivors had overall mild LV dysfunction and moderate RV dysfunction documented by cardiac catheterization. Hemodynamically, nonsurvivors were characterized by lower peripheral systolic blood pressure, higher heart rate, lower ratio of pulmonary to systemic flow, lower RV systolic pressure, and slightly more evidence of renal failure compared with survivors.

To limit the possibility of finding spurious correlations

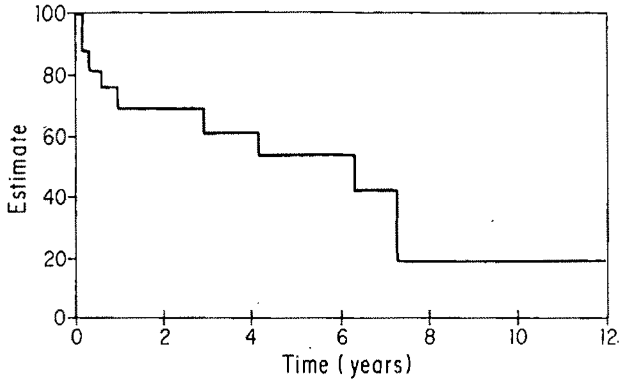

Fig 1. Kaplan-Meier estimate of survival of patients receiving surgical therapy for postinfarction ventricular septal defect.

with surgical survival and given the small population of patients, statistical analysis was limited to four prognostic indicators. The presence or absence of shock, the subjective estimate of LV and RV dysfunction, and the time from diagnosis of postinfarction VSD to operation were tested in a logistic regression model to determine the variable most predictive of subsequent postoperative in-hospital survival. Of these four variables, shock was independently predictive of postoperative survival ($p < 0.01$).

Outcome Analysis

A Kaplan-Meier plot was generated to display the estimate of long-term survival of those patients who survived surgical therapy for postinfarction VSD (Fig 1). Of the 19 survivors, 10 (53%) were alive at the time of last follow-up. The longest survival was 12 years after postinfarction VSD. Seventy percent of the survivors were in New York Heart Association class I or II for angina at the time of last follow-up.

Pathological Findings

The original pathology reports, medical records, and pathological specimens of 15 nonsurvivors of postinfarction VSD were available for review. The pathological findings in these 15 patients were presented in detail in a previous publication [16]. Included in this group were 7 men and 8 women with a mean age of 65 years (range, 51 to 75 years). Seven patients were medically treated, and 8 patients received surgical therapy. The location of infarction was anterior in 8 and inferior in 7 patients. The median time from infarction to appearance of postinfarction VSD was two days. Shock developed in 14 of the 15 patients after the appearance of postinfarction VSD; in 12 patients, shock occurred within 48 hours.

Quantitation of infarct size of the left and right ventricles was determined in 13 hearts. Two hearts were not used because of inadequate preservation. In the left ventricle, infarct size ranged from 13.9% to 48.0% (mean size, 27.2% ± 9.1%). In the right ventricle, infarct size ranged from 1.3% to 71.1% (mean size, 19.8% ± 19.5%).

The amount of left and right ventricle infarcted was examined relative to infarct location. Anterior infarcts involved 32.3% ± 9.9% of the left ventricle and 9.9% ± 8.0% of the right ventricle. In inferior locations, 21.3% ± 6.3% of the left ventricle and 31.4% ± 23.3% of the right ventricle was infarcted. Thus, anterior infarcts involved significantly more of the left ventricle than did inferior infarcts ($p < 0.04$). Conversely, inferior infarcts, although involving a smaller amount of left ventricle, involved a much larger amount of RV myocardium ($p = 0.059$). The Wilcoxon-Mann-Whitney nonparametric two-sample test was used to evaluate the relationship of the amount of right and left ventricle infarcted in anterior and inferior infarctions resulting in postinfarction VSD. When normality cannot be assumed, as with our pathological data, this test is a preferable approach, but resulting p values tend to be slightly conservative. The p value of 0.059 obtained in testing the difference between RV infarction in inferior locations compared with anterior locations in postinfarction VSD represents a strong trend in the data in view of the small sample sizes of the two groups.

Comment

The occurrence of a rupture of the ventricular septum in the aftermath of MI remains a challenge in clinical management despite recent advancements in therapy. The modern treatment of this problem has evolved gradually over the past three decades. For years, treatment was based on knowledge of the time course of infarct healing elucidated by Mallory and colleagues [17]. In their study, it was demonstrated that necrotic tissue is most prominent from the second to sixth day and that collagen fibers, responsible for the strength of the forming scar, do not appear in substantial amount until 12 days after infarction. At 2 months, collagen density is at its greatest, and the infarction is now practically healed.

Based on these observations, it was postulated that if a rupture were to occur, it would most likely be during the first week, possibly in the second week, and very rarely in the third week. During the early 1960s, it was thought that waiting up to 6 weeks after the appearance of a VSD would result in tissue that was firm enough to hold sutures for repair. However, it became clear that relatively few patients could be treated in such a delayed fashion, as most untreated patients were dead at the end of 2 months after rupture. Over the past decade, a much more aggressive surgical approach has been recommended with substantially improved survival [6, 9, 11, 18].

Even now, the details of ideal management, including the optimal time for closure of the VSD and criteria for selecting patients who can benefit substantially from operative intervention, are not well established [19]. In general, the clinical factors that appear to most influence survival after operation are the presence of shock preoperatively, inferior location of the infarction, and RV dysfunction. The presence of shock in postinfarction VSD has been suggested to be largely due to RV impairment [7, 9–14]. Right ventricular dysfunction in postinfarction VSD is probably a consequence of RV infarction, RV ischemia, pressure–volume overload, or a combination of these [12].

Several recent series have examined the role of RV dysfunction, inferior MI, and shock on subsequent death after surgical therapy for postinfarction VSD. Radford and co-workers [9] noted that preoperative cardiogenic shock developed in 55% of 41 patients reviewed, and was the primary determinant of perioperative survival. Postoperative survival was 82% in patients not in shock preoperatively compared with 27% for patients in shock. Shock was unrelated to site of infarction, extent of coronary artery disease, LV ejection fraction, or size of the shunt. However, mean pulmonary artery pressure was lower in patients in shock than in those not in shock. Gross observation of pathological specimens suggested that in patients with inferior infarction, a relationship might exist between shock and extensive RV infarction, whereas in patients with anterior infarction, a relationship might exist between shock and massive septal infarction. Based on these data, it was proposed that RV function was the major determinant of preoperative cardiogenic shock and subsequent survival [9].

Moore and colleagues [11] reviewed the cases of 25 patients with postinfarction VSD and noted that compared with survivors, the nonsurvivors had greater impairment of RV function, greater elevation of RV end-diastolic pressure, and greater mean right atrial pressure. Shock was associated with a 91% mortality and was more common after inferior MI than anterior MI (60% versus 20%). Mortality for inferior MI was 73% compared with 30% for anterior MI. Of 133 variables analyzed, multivariate analysis indicated that nonsurvivors could be identified accurately from effective cardiac index, echocardiographic demonstration of extensive RV and septal dysfunction, elevated mean right atrial pressure, and early onset of postinfarction VSD. These data showed a substantial relationship between RV dysfunction, markedly depressed cardiac index, and increased mortality rate in inferior MIs [11].

Fananapazir and associates [7] reviewed the cases of 50 patients with postinfarction VSD and found that operation in patients with poor RV contraction angiographically carried a higher mortality than operation in patients with good RV performance. Indeed, 80% of patients with good RV contraction survived compared with only 24% of patients with poor RV function. Furthermore, poor RV free wall contraction was present in 44% of anterior infarctions as well as 71% of inferior infarctions. Anterior MI carried a better hospital survival rate than inferior MI (67% versus 31%).

Kereiakes and colleagues [13] examined the hemodynamic profile and clinical course of 4 patients with postinfarction VSD associated with RV infarction. A syndrome was described characterized by a hemodynamic profile consistent with biventricular dysfunction and progressive hemodynamic deterioration.

Grose and Spindola-Franco [14] examined 8 patients with postinfarction VSD and noted that all had severe RV dysfunction angiographically. All 8 patients experienced rapid deterioration requiring mechanical and inotropic support after postinfarction VSD. Subsequently, biventricular infarction was confirmed at operation. Seven of the 8 patients died, and RV dysfunction was considered to be a contributing factor to death in the majority of them. Goldman and coauthors [12] reported two cases of acute inferior MI complicated by postinfarction VSD and severe RV dysfunction. Right ventricular infarction was found in both patients at operation. Although severe dysfunction was manifested preoperatively, RV ejection fraction improved significantly after surgical correction of the postinfarction VSD.

Jones and associates [10] reported data on 60 patients undergoing surgical repair of postinfarction VSD. Inferior location of MI was associated with a 58% mortality compared with 25% in anterior locations. Furthermore, early survival was favored by good preoperative RV function (assessed angiographically) but was not influenced by LV function. Conversely, long-term survival was favored by preserved preoperative LV function but was not affected by preoperative RV function.

Our data support these conclusions. In a logistic regression model, we found shock to be the primary factor predictive of postoperative survival; RV and LV function and time from diagnosis to operative repair were not independently significant. Shock was greater in anterior infarction compared with inferior infarction, yet mortality was greater in the latter group. The pathological findings indicate that compared with anterior MI, inferior MI resulting in postinfarction VSD is characterized by a relatively small amount of LV infarction but a significantly larger amount of RV infarction. Therefore, in addition to shock, inferior location associated with increased RV infarction may result in greater postoperative mortality. Establishing a preoperative distinction between survivors and nonsurvivors using ventriculography to assess RV dysfunction was not possible. Right ventricular dysfunction was moderately severe in most patients.

To update outcomes with modern therapy for postinfarction VSD, a number of published surgical series [6–8, 10–14, 18–32] were reviewed (Table 3). A total of 585 patients were reported in 23 series published from 1973 to

Table 3. Summary of Data From Review of 23 Surgical Series Involving Postinfarction Ventricular Septal Defect[a]

Variable	Value
No. of patients	585
Average age (yr)	64
Location of infarction (%)	
Anterior	59
Inferior	41
Sex (%)	
Male	65
Female	35
Therapy	
Medical (% survival)	50 patients (2)
Surgical (% survival)	535 patients (57)
Follow-up	238 patients
NYHA class I, II (%)	95

[a] The references are as follows: 6–8, 10–14, and 18–32. They were published between 1973 and 1987.

NYHA = New York Heart Association.

1988. Sixty-five percent of the patients were male, 35% were female, and the mean age was 64 years. Fifty-nine percent of infarctions were anterior and the remaining, inferior. Fifty patients were treated medically. One patient in this group lived 4.5 years after postinfarction VSD. The remainder of the nonsurgical group all died within 1 year of diagnosis. Of the 535 patients treated surgically, there was an overall 43% in-hospital mortality rate, which is similar to the rate of 42% in our surgically treated group. This mortality rate includes all patients irrespective of the presence or absence of shock, timing of operation, and location of infarction. Follow-up was available at various time points on 238 patients; 95% of them were in New York Heart Association class I or II for angina.

In summary, the results of the present study show that postinfarction VSD is associated with progressive development of heart failure or shock. The results confirm previous reports indicating a virtually 100% mortality associated with nonoperative therapy. Irrespective of LV or RV function or timing of operation, the development of shock is the single most important predictor of survival. If shock is allowed to develop, mortality is significantly increased. In addition, inferior location of infarction may be associated with greater mortality because of associated RV dysfunction and infarction. The results of this study and previously published reports indicate that long-term survival and excellent functional recovery can be achieved in patients undergoing successful surgical repair. An extremely important clinical goal is to establish the diagnosis of postinfarction VSD before the onset of shock.

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REVIEW OF RECENT BOOKS

Cardiac Valve Allografts 1962–1987. Current Concepts on the Use of Aortic and Pulmonary Allografts for Heart Valve Substitutes

Edited by A. C. Yankah, R. Hetzer, D. C. Miller, D. N. Ross, J. Somerville, and M. H. Yacoub
New York, Springer-Verlag, 1988
394 pp, illustrated

Reviewed by Pedro J. del Nido, MD

This recently published book contains the proceedings of the Symposium on Current Concepts on the Use of Aortic and Pulmonary Allografts for Heart Valve Substitutes, which was held in Berlin in September of 1987. The symposium was organized by the German Heart Center and invited speakers included Mr Donald Ross and Sir Brian Barratt-Boyes as well as a long list of eminent surgeons, pathologists, and immunologists all expert in the field of cardiac valve allografts. The book is a compendium of papers that were presented at this meeting subgrouped into six different subheadings involving procurement and preservation techniques, immunology of allografts, surgical techniques for implantation of aortic and pulmonary valve substitutes, and the long-term results with both antibiotic-treated and cryopreserved allografts. The first paper is a review of the evolution of the field by Mr Donald Ross and is a summary of the many contributions that were made in the past 25 years to this field, as well as a summary of his experience with the use of antibiotic-preserved allografts and autografts. At the end of the text a similar paper is presented by Sir Brian Barratt-Boyes, in which he summarizes his 25 years of experience with allografts in New Zealand.

Overall the book is very well organized and well written with the important subdivisions assisting the reader in obtaining the information needed. All the papers are from authors who are experts in their field and provide the most comprehensive and up-to-date information in this area. The information that is provided should be of interest to individuals with a variety of backgrounds including cell biologists, immunologists, and cardiac surgeons involved in either congenital or acquired cardiac surgery, as well as pediatric and adult cardiologists who may be involved in the postoperative follow-up of these patients. The chapters involving the surgical techniques are well written and include clear and useful illustrations of the operations. They would be of great value to practicing congenital and adult cardiac surgeons.

Although the majority of papers are targeted for cardiac surgeons, this book should be of great interest to cell biologists involved in cryopreservation as well as cardiologists who need up-to-date information regarding the long-term results with allografts.

Chicago, Illinois

Ten Years' Experience With the St. Jude Medical Valve Prosthesis

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Records of 1,298 consecutive patients who had received the St. Jude Medical prosthesis were reviewed (713 male and 585 female patients; mean age, 61.79 ± 13.4 years). Early mortality was 5.7% (74 patients). Ninety-three percent complete follow-up was accomplished for the 1,224 patients who left the hospital (4,306.50 patient-years). One hundred ninety-two of these patients died, a late mortality of 16.9%. Sixty-four patients experienced thromboembolic episodes (17 major and 35 permanent). Twenty-four patients had anticoagulant-related bleeding, 4 had valve thrombosis, 7 had prosthetic valve endocarditis, 9 had paravalvular leak, and 10 underwent reoperation. There was no structural valve failure in this series. Twenty-two of the 118 patients who had valve-related complications died; another 15 patients died of sudden and unknown causes. Therefore, the total number of valve-related deaths was 37. Of those patients who survived, New York Heart Association functional class improved significantly (98% in classes II and III preoperatively and 96% in classes I and II postoperatively). Linearized rates for thromboembolism, valve thrombosis, and anticoagulant-related bleeding were 1.49% ± 0.19%, 0.09% ± 0.05%, and 0.56% ± 0.11%/100 patient-years, respectively. The actuarial estimate of incidence free from all complications, operative death, and valve-related death was 66.9% ± 8.2% at the end of 9 years. In spite of old age and advanced heart disease, the patients who received the St. Jude Medical prosthesis had very good results over a 10-year period.

(Ann Thorac Surg 1989;47:831–7)

The St. Jude Medical valve was first used clinically in 1977. Compared with other available prostheses, this valve has unique features. Its bileaflet central-flow design provides a lower transvalvular pressure gradient than other mechanical valves, and the total pyrolytic carbon construction suggested it would be durable and thromboresistant. Earlier reports [1–4] indicate that, as expected, the valve has performed well with a low incidence of valve-related problems.

Since the first implantation of this valve at our institution, we have adopted the St. Jude Medical prosthesis as the valve of choice and have placed it in more than 1,400 patients. This is an analysis of an experience covering 10 years. It includes 1,298 patients who received valve replacements, and deals with the performance of the prosthesis, its complications, and survival rates of patients.

Material and Methods

During the 10-year period between October 1977 and October 1987, 1,298 patients received St. Jude Medical valves at our institution. There were 713 male and 585 female patients ranging in age from 1 year to 89 years. All patients were included in this review whether the operation was done on an elective or emergency basis, and whether it was a first operation or a reoperation. Preoperative angiographic and hemodynamic evaluation was carried out in all patients except those who experienced decompensation during the cardiac catheterization procedure. Preoperatively, 43.6% of patients were in New York Heart Association functional class II and 54.6%, in class III.

Congestive heart failure was the main indication for valve replacement, accounting for 85% of the patient population. Congestive heart failure in association with angina was not necessarily a contraindication to operation as long as the overall left ventricular function was reasonably preserved. Of the 1,298 patients, 809 had either isolated aortic valve replacement (AVR) (469 patients) or isolated mitral valve replacement (MVR) (340 patients), and 75 patients had double-valve replacement. Three hundred sixty-three patients or 28% had combined coronary artery bypass grafting (CABG) and valve replacement (229 AVR + CABG, 124 MVR + CABG, and 10 double-valve replacement + CABG). The remaining 51 had miscellaneous procedures performed in addition to valve replacement, for example, closure of acquired ventricular septal defect, resection of left ventricular aneurysm, replacement of ascending aortic aneurysm, or carotid endarterectomy. Details of the procedure, age, and sex distribution are presented in Table 1.

Operative techniques were standardized and included total cardiopulmonary bypass with a bubble or membrane oxygenator and moderate hypothermia. In most of the procedures, potassium crystalloid cardioplegia and a single aortic cross-clamp were used. Details of cardiopulmonary bypass, myocardial protection, and valve implantation technique have been described elsewhere [5, 6].

Presented at the Thirty-fifth Annual Meeting of the Southern Thoracic Surgical Association, Marco Island, FL, Nov 10–12, 1988.

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Table 1. Operative Procedures, Sex, and Age Distribution of Patients[a]

	Sex		
Procedure	Male	Female	Age[b] (yr)
AVR	295	174	61.6 ± 14.5
AVR + CABG	161	68	67.9 ± 8.2
MVR	135	205	57.6 ± 0.9
MVR + CABG	70	54	64.8 ± 8.2
DVR	31	44	59.8 ± 12.3
DVR + CABG	3	7	67.7 ± 6.3

[a] Fifty-one additional patients underwent valve replacement plus various miscellaneous procedures. [b] Data are shown as the mean ± the standard deviation.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; DVR = double-valve replacement; MVR = mitral valve replacement.

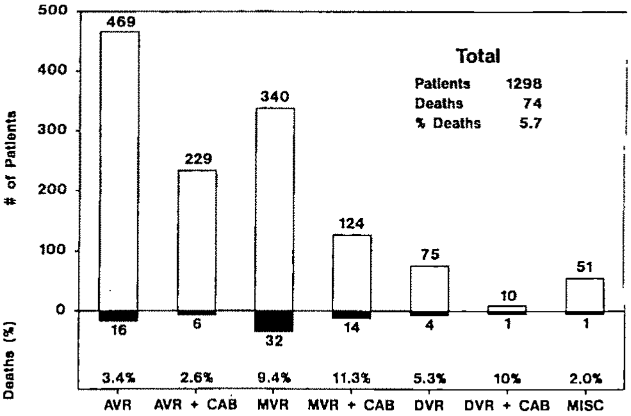

Fig 1. Number of patients in and operative mortality for each subset. (AVR = *aortic valve replacement;* CAB = *coronary artery bypass grafting;* DVR = *double-valve replacement;* MISC = *miscellaneous;* MVR = *mitral valve replacement.)*

Subcutaneous administration of heparin sodium was started on the first postoperative day and continued until the prothrombin time level could be regulated appropriately. The patient was discharged from the hospital between eight and 11 days after operation.

To describe survival rates and the incidence of valve-related complications, standard nonparametric actuarial Kaplan-Meier and linearized statistical techniques were calculated, although we realize that these complications do not occur on a linear basis. Actuarial probability estimates are presented as cumulative proportions surviving and 95% confidence levels at 9 years. Linearized rates are presented with the standard error. The format of this report follows recent guidelines for reporting morbidity and mortality after cardiac valve operations as proposed by The Society of Thoracic Surgeons [7].

Results

Early Mortality

Seventy-four of the 1,298 patients died either within 30 days after operation or during the hospitalization in which the operation was performed, a mortality rate of 5.7% (Fig 1). There was little difference in early mortality between the group having isolated AVR and the group having AVR + CABG. However, the operative mortality for the patients having AVR was lower than that for patients having either isolated MVR or MVR + CABG.

Follow-up Studies

One thousand two hundred twenty-four patients were discharged from the hospital and followed periodically by family physicians, cardiologists, or cardiac surgeons. At the time of this study, patients were contacted directly by questionnaire or telephone communication or through the referring physician. Eighty-five patients (6.9%) could not be located and were considered lost to follow-up. Many attempts were made to locate them to achieve more complete follow-up as suggested by the guidelines, but to no avail. Therefore, 93% of all the patients were included in this study. The total follow-up was 4,306.50 patient-years.

Late Mortality

One hundred ninety-two patients (16.9%) had died by the last date of follow-up. The late mortality is shown in Figure 2. The causes of late death have been grouped into three categories: (1) valve related (37 patients), (2) noncardiac related, such as malignancy (23%), respiratory failure or pulmonary emboli, ruptured aneurysm or peripheral vascular disease, and automobile accident or other trauma (52 patients), and (3) cardiac related (103 patients).

Among the patients who died of valve-related complications, the cause of death in 18 was thromboembolism or anticoagulant-related bleeding. Two patients died of valve thrombosis, 1 with a valve in the tricuspid position and the other, in the mitral position. One patient died during antibiotic therapy for prosthetic valve endocarditis, and 1 patient died during reoperation for a paravalvular leak secondary to prosthetic valve endocarditis. Another 15

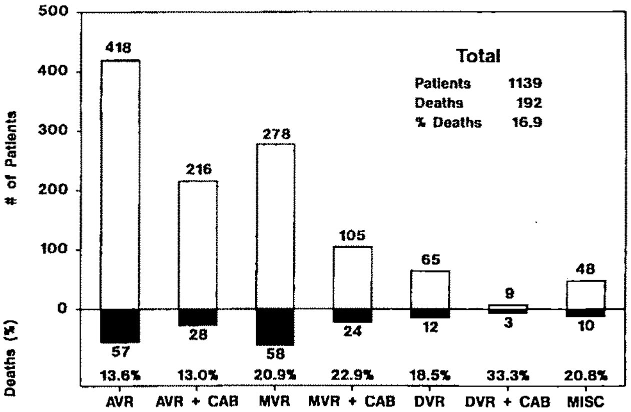

Fig 2. Number of patients in and late mortality for each subset. (AVR = *aortic valve replacement;* CAB = *coronary artery bypass grafting;* DVR = *double-valve replacement;* MISC = *miscellaneous;* MVR = *mitral valve replacement.)*

patients died of a sudden and unexpected cause, for a total of 37 valve-related deaths. There were no deaths from structural deterioration or critical hemolysis. Cardiac-related causes of death were either progressive atherosclerosis or congestive heart failure. The causes of valve-related death by procedure are listed in Table 2.

Valve-Related Complications

The incidence of valve-related complications is shown in Table 3.

THROMBOEMBOLISM. Sixty-four patients sustained a thromboembolic event. The overall incidence of thromboembolism was 1.49% ± 0.19%/100 patient-years. The linearized rate was 1.09% ± 0.27%, 1.75% ± 0.39%, and 1.64% ± 0.82%/100 patient-years for the AVR, MVR, and double-valve replacement groups, respectively. Of these 64 patients, 17 had major episodes of thromboembolism, and 35 sustained permanent valve-related impairment.

ANTICOAGULANT-RELATED BLEEDING. Twenty-four patients were confirmed to have had transfusions for anticoagulant-related bleeding. However, for obvious reasons not related to the valve or anticoagulation, more patients received transfusions during the postoperative course. These were patients who underwent other operations such as hip replacement, colon resection, or for trauma. In accordance with the new guidelines [7], these patients were excluded from our report.

Nine of the 24 patients died of this complication. The incidence of complications from anticoagulants was 0.56% ± 0.11%/100 patient-years.

Table 2. Causes of Valve-Related Death by Procedure[a]

Procedure	Cause	No. of Patients
AVR	Cerebral hemorrhage	1
	Gastrointestinal bleeding	2
	Thromboembolism	1
AVR + CABG	Cerebral hemorrhage	3
	Thromboembolism	1
MVR	Cerebral hemorrhage	3
	Coronary emboli	1
	Thromboembolism	2
	CHF secondary to paravalvular leak (mitral)	1
MVR + CABG	Late prosthetic valve endocarditis	1
	Thromboembolism	4
	Valve thrombosis	1
Miscellaneous	Valve thrombosis (tricuspid)	1
Total		22

[a] Deaths were documented either by postmortem examination or clinical evaluation. The 15 patients who died of sudden and unexpected causes were excluded from this table.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CHF = congestive heart failure; MVR = mitral valve replacement.

Table 3. Valve-Related Complications and Deaths[a,b]

Variable	Incidence of Complications	No. of Deaths
Thromboembolism	64 (5.6)	9 (0.8)
Valve thrombosis	4 (0.4)	2 (0.2)
Paravalvular leak	9 (0.8)	1 (0.1)[c]
Endocarditis	7 (0.6)	2 (0.2)[c]
Reoperation	10 (0.9)	1 (0.1)[c]
Anticoagulant-related bleeding	24 (2.1)	9 (0.8)
Structural deterioration	0	0
Sudden, unexplained death	0	15 (1.3)
Total	118 (10.4)	37 (3.2)

[a] Numbers in parentheses are percentages of 1,139 patients surviving operation and included in follow-up. [b] No deaths or complications were caused by mechanical failures. [c] The same patient had prosthetic valve endocarditis, a paravalvular leak, and reoperation.

VALVE THROMBOSIS. Valve thrombosis developed in 4 patients, in the mitral position in 3 and in the tricuspid position in 1. Two died (1, tricuspid, and 1, mitral), and both had definite proof of pannus formation, 1 at the tricuspid and 1 at the mitral orifice. The other 2 patients had suggestive evidence of thrombosis by clinical findings and noninvasive studies. The condition of these patients subsequently improved without surgical intervention. The linearized incidence of valve thrombosis was 0.09% ± 0.05%/100 patient-years.

PROSTHETIC VALVE ENDOCARDITIS. Seven patients had prosthetic valve endocarditis. In 4 it occurred early; the other 3 had evidence of endocarditis late after operation. Appropriate antibiotics cured 4 of the patients. One patient died during antibiotic therapy, and in the other 2, a major paravalvular leak developed and necessitated operation. The linearized incidence of prosthetic valve endocarditis was 0.16% ± 0.06%/100 patient-years.

NONSTRUCTURAL DYSFUNCTION. Nine patients had paravalvular leaks to various degrees. Six had symptoms severe enough to necessitate surgical intervention to repair the leaks. In the 3 others, the diagnosis was confirmed by physical examination and Doppler flow study. The linearized incidence of nonstructural dysfunction was 0.21% ± 0.07%/100 patient-years.

STRUCTURAL DETERIORATION. There was no change in valve function resulting from an intrinsic abnormality causing stenosis or unusual regurgitation. There was also no structural failure such as a wear or stress fracture of any part of the prosthesis. There was no report of clinically important hemolytic anemia or hemolysis in any of these patients.

Consequence of Morbid Events

REOPERATION. There were 10 reoperations. Six were done to repair a paravalvular leak due to either prosthetic valve

Table 4. Actuarial Estimates of Percentage of Patients Free From Valve-Related Complications and Deaths

Complications and Deaths	Entire Group[a]	AVR[b]	MVR[b]	DVR[b]
Thromboembolism	87.9 ± 3.5	92.0 ± 4.4	88.5 ± 5.3	90.3 ± 9.4
Valve thrombosis	99.8 ± 0.4	100	100	100
Paravalvular leak	99.2 ± 0.6	100	97.7 ± 1.8	97.3 ± 5.3
Reoperation	99.1 ± 0.6	99.8 ± 0.5	97.0 ± 2.1	100
Anticoagulant-related bleeding	93.9 ± 5.7	97.7 ± 2.0	96.8 ± 2.6	100
Valve endocarditis	99.2 ± 0.7	98.8 ± 1.6	98.9 ± 1.3	100
Structural failure	100	100	100	100
Permanent valve-related impairment	93.4 ± 2.6	96.0 ± 3.4	94.5 ± 3.9	92.2 ± 8.7
Valve-related death	94.4 ± 2.1	97.1 ± 2.2	95.4 ± 3.2	94.0 ± 8.2
Operative death and permanent disability	88.0 ± 2.7	92.6 ± 3.7	85.3 ± 4.7	87.3 ± 9.6
Operative death, valve-related death, and valve-related impairment	84.4 ± 3.1	90.5 ± 4.0	82.4 ± 5.1	81.8 ± 11.7
Operative death, valve-related death, and complications	66.9 ± 8.2	82.2 ± 5.3	72.3 ± 6.3	77.7 ± 12.5

[a] This is at 9 years. [b] This is at 6 years.

AVR = aortic valve replacement; DVR = double-valve replacement; MVR = mitral valve replacement.

endocarditis or a technical failure of the original operation. Two patients underwent explantation because of prosthetic valve endocarditis, 1 patient had a reoperation for possible mechanical obstruction of the aortic valve 1 week after implantation, and another patient had reoperation for cardiac transplantation. The linearized incidence of reoperation was 0.06% ± 0.06%/100 patient-years.

VALVE-RELATED MORTALITY. There were 37 valve-related deaths, 22 of them definitely proven to be due to valve-related complications (see Table 3). Twenty of these patients died of thromboembolism, valve thrombosis, or anticoagulant-related bleeding. One patient died during antibiotic treatment for prosthetic valve endocarditis and in another patient with prosthetic valve endocarditis, a major paravalvular leak developed. That patient died at the time of reoperation. Fifteen other patients died of sudden, unexplained, and unexpected causes. The linearized incidence of valve-related death was 0.86% ± 0.14%/100 patient-years.

PERMANENT VALVE-RELATED IMPAIRMENT. There were 35 permanent functional deficits resulting from a thromboembolic event. Seventeen of these patients sustained a major neurological impairment, but, to date, residual neurological deficits in the other 18 patients have not caused any major difficulties in their routine daily activities. The linearized incidence of valve-related impairment was 0.81% ± 0.14%/100 patient-years.

COMBINATIONS OF MORBID CONSEQUENCES. Including operative deaths and reoperations, there were 84 valve-related incidents. Combining operative deaths and permanent disabilities gives a total of 109 valve-related incidents, 74 of which were hospital deaths and 35 of which involved permanent major and minor neurological deficits. Combining operative deaths, valve-related deaths, and all nonfatal valve-related morbid events gives a total of valve-related morbidity and mortality of 229: 64 thromboembolic events, 24 anticoagulant-related bleeding events, seven prosthetic valve endocarditis events, ten reoperations, four valve thromboses, nine paravalvular leaks, 74 early deaths, and 37 valve-related deaths.

PATIENTS FREE FROM DEATH AND COMPLICATIONS. Actuarial freedom from death and complications was computed. Actuarial estimates of the percentage of patients free from death and complications 6 and 9 years after operation are summarized in Table 4.

PATIENT SURVIVAL. Two sets of survival curves were constructed from 10-year actuarial estimates. The first curve (including both early and all late deaths) is shown in Figure 3A. The 6-year survival was 78.4% ± 5.2% in the AVR group, 73.8% ± 12.4% in the double-valve replacement group, and 64.9% ± 6.8% in the MVR group.

When early deaths were eliminated (Fig 3B), the 6-year survival rate was close between the AVR and double-valve replacement groups (81.3% ± 5.2% and 77.9% ± 12.4%, respectively). However, the MVR group had only a 71.9% ± 7.1% estimated survival at 6 years.

Using the Mantel-Haenszel test statistics, the over-time survival experience of the AVR group is significantly better than that of the MVR group ($p > 0.01$) and that of the AVR + CABG group is significantly better than that of the MVR + CABG group ($p > 0.01$). However, no significant difference was found between the MVR group and the double-valve replacement group.

Comment

During the past 10 years, the St. Jude Medical prosthesis has been the cardiac valve of choice in many institutions, and has represented a valuable alternative to currently

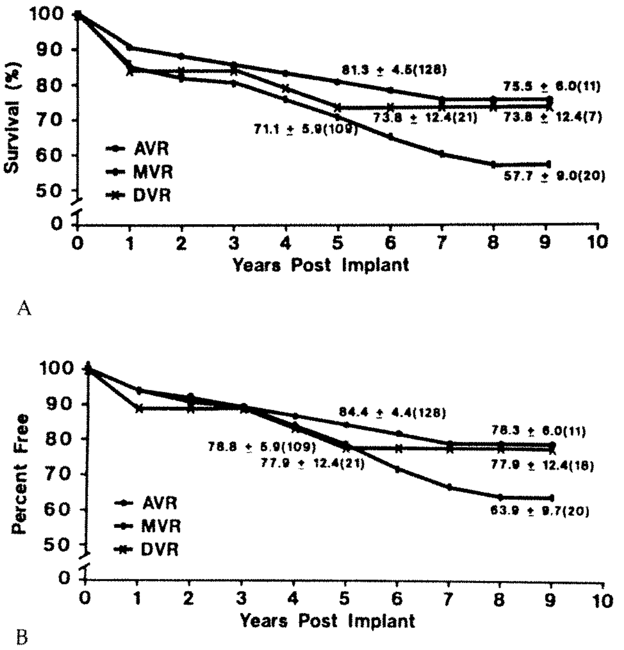

Fig 3. Actuarial survival curves for the entire group of patients (A) including operative and late deaths and (B) excluding operative deaths. (AVR = *aortic valve replacement;* DVR = *double-valve replacement;* MVR = *mitral valve replacement.)*

available mechanical and bioprosthetic devices. The present clinical assessment was carried out to evaluate the long-term performance characteristics of the St. Jude Medical valves and patient survival at 10 years, and to provide data for further comparison with other commonly used prostheses.

Lillehei [8] reviewed a 5-year experience with the St. Jude valve in a multicenter study, and suggested that the results of prosthetic valve function, calculated survival, and freedom from thromboembolism are as good as—if not better than—the experience with other types of valves, and that longer-term follow-up evaluation would be needed for further comparisons.

October 1987 marked the tenth anniversary of the St. Jude Medical prosthesis. By that time, a total of 1,298 consecutive patients who were operated on by the same group of surgeons were available for a first 10–year follow-up study. The early mortality of 5.7% in this group compared favorably with the 6.6% in our previous report [9]. Operative deaths after AVR remain low, in the 2.5% to 3.5% range; this finding has not changed from previous reports. This is also true in the isolated MVR group where the early mortality remained in the 8% to 9.5% range. However, the incidence of early death after MVR + CABG has improved to 11% from 17%. The reason for this improvement in this subset is not quite clear. The early mortality after double-valve replacement alone and double-valve replacement + CABG remains unchanged from our results at 6 years [9].

Late mortality has increased from 7.7% at 6 years to 16.9% at 10 years. The incidence of late death due to ongoing atherosclerosis in patients who are now 10 years older increased substantially, but the incidence of valve-related deaths remains unchanged at less than 2%. Comparing the incidence of late death between this result and the results reported at 6 years shows an increase from 6.2% to 13.6% for AVR, 6.3% to 13.0% for AVR + CABG, 7.9% to 20.9% for MVR, 6.7% to 22.9% for MVR + CABG, 15.8% to 18.5% for double-valve replacement, and 18.2% to 33.3% for double-valve replacement + CABG. Patients in the last group again are not doing well at this time of follow-up; 33% have died, and of those who are alive, left ventricular function has not substantially improved after surgical correction.

When causes of late death were analyzed, it was found that more than 50% of the patients died of ongoing atherosclerosis and ventricular failure unrelated to the prosthesis, and 37 patients or 3.2% of the patients died of various reasons related to prosthetic valve complications. Nine of these patients died of a thromboembolic event. For the past 4 years, the incidence of death due to thromboembolism has remained the same at less than 1% [1, 9].

Nine patients also died of anticoagulant-related bleeding, and this 0.8% incidence has increased from the previously reported 0.3% [1]. Two patients from the entire group died of valve thrombosis during the first 5 years after operation. Two patients died as a result of prosthetic valve endocarditis, 1 during the course of antibiotic treatment and the other after reoperation for a paravalvular leak. It is important to note that with this prosthesis, there were no deaths due to structural deterioration or hemolysis. The actuarial rate of freedom from late death was 71.1% ± 4.4%.

Thromboembolic events and bleeding caused by anticoagulants represented the majority of complications after prosthetic valve replacement. After the development of a new prosthesis with improved hemodynamics and materials that lessened thrombogenicity, the rate of thromboembolic events gradually declined. In this study, 64 patients sustained a thromboembolic complication. The linearized incidence of thromboembolism in the entire group was 1.49% ± 0.9%/100 patient-years, and that compares favorably with the previous incidence of 1.78%/100 patient-years [1]. The incidence of thromboembolism arising from the aortic valve was approximately 1% and was less than 2% for the mitral position or the two locations combined. The incidence of freedom from thromboembolism was computed, and the actuarial curves for patients free from thromboembolism after AVR, MVR, or double-valve replacement were constructed (Fig 4). At 6 years, the cumulative proportion free from thromboembolism was 92.0% ± 4.4% for the AVR, 88.5% ± 5.3% for the MVR, and 90.3% ± 9.4% for the double-valve replacement groups.

As far as anticoagulant-related bleeding is concerned, a new guideline recently published in *The Annals [7]* provides a better method of reporting the incidence of bleeding during the postoperative period. Only the major incidence of bleeding (required transfusion or death) was reported in this study, and the usual transfusions given during a major surgical procedure were excluded. With this approach, the incidence of anticoagulant-related

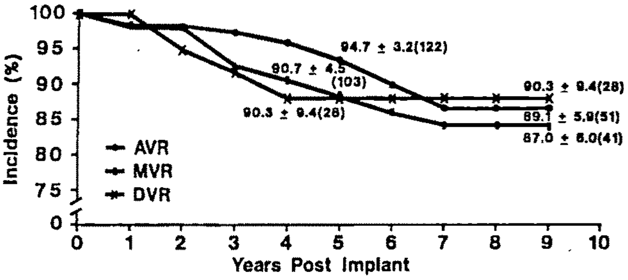

*Fig 4. Actuarial curves for patients free from thromboembolism after aortic (*AVR*), mitral (*MVR*), and double-valve replacement (*DVR*).*

bleeding dropped substantially from the previous report, and the cumulative proportion free from anticoagulant-related bleeding at 9 years was 93.9% ± 5.7%.

There was no new incidence of valve thrombosis since the last survey 5 years ago [1, 9]. The cumulative proportion free from valve thrombosis at 6 years was 99.8% ± 0.4%. The nearly central flow, the almost complete absence of stasis downstream, and the use of highly polymerized pyrolytic carbon for valve parts would tend to predict the low rate of thromboembolism seen in this study.

Prosthetic valve endocarditis is an exceedingly serious complication in patients who have had prosthetic valve replacement. Seven patients had prosthetic valve endocarditis, 4 of whom were cured with appropriate antibiotics. The incidence of prosthetic valve endocarditis in our series is rather low and has not changed since the previous report (0.7% versus 0.5%). The valve design and the increased probability of prosthetic valve sterilization may play an important role in the low incidence of prosthetic valve endocarditis.

As far as nonstructural dysfunction is concerned, a paravalvular leak developed in 9 patients. Two leaks were the result of prosthetic valve endocarditis, and the other seven were the result of technical difficulties at the time of operation, either residual calcification or poor native tissue of the annulus. The entire incidence of paravalvular leak remains 0.21% ± 0.07%/100 patient-years. Valve suturing techniques probably play an important role in this because interrupted everted mattress stitches could provide better approximation between the sewing ring and annulus tissue [6].

Hemolysis usually is of no clinical importance in the intact function of the St. Jude Medical prosthesis. It has, however, been of concern to some authors and to the professional staff of St. Jude Medical, Inc (personal communications, 1988). Hemolysis has been reported in patients with or without paravalvular leak [10]. The etiology is not quite clear, and hemolysis did not occur in our practice. However, immediately after operation, brief but major hemolysis and hemolytic anemia from lethal and sublethal red blood cell damage caused by extracorporeal circulation have been observed. None of the patients had any clinical evidence of continuing hemolysis at the time of discharge or during this follow-up study.

All of the ten reoperations were unrelated to structural deterioration. The incidence of freedom from reoperation in this series was 99.1% ± 0.6%/100 patients years. This finding strongly supports the early expectation that the St. Jude Medical prosthesis would be a durable valve.

Thirty-seven valve-related deaths occurred. There was definite evidence that 22 of these patients died of valve-related complications. The other 15 patients died of sudden, unknown, and unexpected causes, but most likely the major causes were arrhythmias. The linearized incidence of all valve-related deaths was 0.86% ± 0.14%/100 patient-years, which is comparable to that in the previously reported series.

In this series, 35 patients sustained a permanent neurological deficit as a result of thromboembolic events or anticoagulant-related bleeding. The linearized incidence of valve-related impairment was 0.81% ± 0.14%/100 patient-years, and the actuarial estimate of freedom from valve-related impairment was better than 90% after 9 years. When valve-related impairment and operative death were combined, the actuarial estimate showed that more than 65% of the patients were doing well at the time of this follow-up. At 10 years, nearly two thirds of the entire group of patients remain free from operative death, valve-related death, or other complications.

As far as patient survival is concerned, 75.5% of the patients in the AVR group, 73.8% of the patients in the double-valve replacement group, and 57.7% of the patients in the MVR group are alive at 10 years (see Fig 3A). Not only do these patients enjoy a complication-free status, but their life-style is also substantially improved. According to this survey, 96% of them are now in New York Heart Association functional classes I and II. The percentages assigned to these two classes may not be justified scientifically for several reasons: the study was conducted retrospectively; there was no uniform documentation of functional class in the individual patient's records prior to operation; and approximately 70% of the answers were completed.

In conclusion, the 10-year follow-up study of 1,139 patients who were discharged from the hospital after receiving the St. Jude Medical prosthesis revealed that the valve has a low incidence of valve-related complications (2.7% ± 0.25%/100 patient-years) and deaths (0.86% ± 0.14%/100 patient-years). To date, the valve has proved to be durable and has had no incidents of structural failure. The occurrence of thromboembolism and anticoagulant-related bleeding has been low. As far as patients are concerned, nearly three fourths of the patients in the AVR or double-valve replacement group and more than half of the patients in the MVR group are alive and well, with the majority (96%) classified in New York Heart Association functional classes I and II. The linearized incidence of late death, however, is high (4.46% ± 0.32%/100 patient-years); this reflects the inclusion of the elderly and high-risk patients in our series, as more than half of the patients who had died at the time of this follow-up had ongoing atherosclerosis or left ventricular failure, or died of other natural causes but not valve-related complications. These findings were also confirmed by the Cox multiple regression analysis, which identified age as strongly associated with their fatal outcome.

When comparisons of the incidence of valve complications and patient survival were made between the St. Jude Medical, Hancock bioprosthesis [11, 12], Starr-Edwards ball valve [13, 14], and Björk-Shiley spherical-disc prosthesis [15], the data showed the clear superiority of the St. Jude Medical prosthesis for its durability, low thrombogenicity, and lower incidence of prosthetic valve endocarditis. The incidence of patients free from thromboembolism is as good as that with bioprostheses. After 10 years, the survival estimates for patients with the St. Jude Medical prosthesis are comparable to those for patients with other prostheses despite a higher incidence of nonvalve-related deaths in the St. Jude Medical series.

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Transsternal Radical Thymectomy for Myasthenia Gravis: A 15-Year Review

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Thymectomy is an accepted therapeutic modality for patients with myasthenia gravis. The selection of patients for operation and the surgical approach are controversial. We reviewed 52 patients (aged 18 months to 82 years; mean age, 34 years) treated with transsternal radical thymectomy between 1972 and 1987. Patients were symptomatically staged according to the modified Osserman classification. There was one hospital death and postoperative follow-up was obtained on 51 patients. Improvement after thymectomy was observed in 3 of 11 patients (27%) in Osserman stage I, 16 of 25 patients (64%) in Osserman stage IIA, and 13 of 15 patients (86%) in combined Osserman stages IIB, III, and IV. Preoperative Osserman stage, patient sex, and thymic histology correlated with postoperative clinical response. Transsternal radical thymectomy is effective therapy for myasthenia gravis. Sustained improvement is obtained in patients with moderate and advanced disease. The majority of patients with ocular disease do not benefit from operation.

(Ann Thorac Surg 1989;47:838–40)

Surgical removal of the thymus gland for myasthenia gravis has gained increasing popularity since Blalock and co-workers introduced this treatment in 1939 [1]. Patients with myasthenia gravis who undergo thymectomy demonstrate a superior response with respect to symptoms and medication requirements when compared with those patients treated nonsurgically [2]. Controversy persists, however, over the proper selection of patients and the optimal surgical approach.

This report reviews our experience with thymectomy for myasthenia gravis using the transsternal approach. A variety of preoperative clinical variables were assessed to determine if patient selection could have an effect on long-term clinical results.

Material and Methods

All clinical records of patients with myasthenia gravis who underwent thymectomy at the New England Medical Center Hospital within the 15-year interval from 1972 through 1987 were reviewed. Complete follow-up information was obtained through telephone contact or questionnaire completed by the patient or his or her referring physician.

Patients were clinically staged according to the modified Osserman classification [2] as follows: I, ocular symptoms only; IIA, mild generalized symptoms; IIB, moderate generalized symptoms with prominent bulbar or respiratory involvement; III, acute, fulminating myasthenia gravis; and IV, muscle wasting present. Patients were classified postoperatively as in remission (asymptomatic, no medications), improved (lower Osserman stage or same stage on fewer medications), improved (lower Osserman stage or same stage on fewer medications), unchanged, or symptomatically worse.

Clinical variables consisting of patient age, sex, preoperative Osserman stage, preoperative acetylcholine receptor antibody titers, thymic histology, duration of symptoms, and duration of postoperative follow-up were examined to determine if they correlated with postoperative response.

Statistical methods included Bartholomew's test for increasing proportions and Fisher's exact text with Bonferroni correction, followed by multiple regression analysis. A p value of less than 0.05 was considered significant.

Results

Data were analyzed for 52 patients with myasthenia gravis who underwent radical transsternal thymectomy. Follow-up was obtained on 51 patients between 4 months and 15 years (mean follow-up, 46 months) after thymectomy. In this series there were 19 male patients (37%) and 33 female patients (63%). The mean age at the time of operation was 34 years with an age range of 18 months to 82 years.

Patient age, preoperative duration of symptoms, and postoperative length of follow-up did not correlate with response to thymectomy (patients in remission or improved). Patient sex did correlate with response, with 72% of female patients responding versus only 47% of males ($p < 0.05$). Combining all Osserman stages, there

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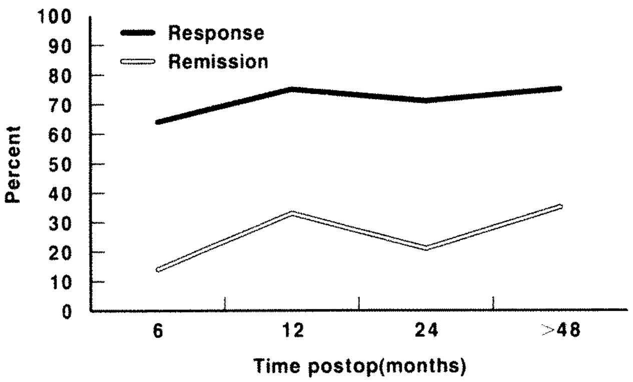

Fig 1. Postoperative response (patients in remission and improved) versus duration of follow-up after thymectomy.

was no significant difference in response rates between those patients with less than 2 years of follow-up and patients more than 4 years after thymectomy (Fig 1).

Preoperative Clinical Status

There were 11 patients with preoperative Osserman stage I, 26 with stage IIA, and 15 (29%) patients with moderate or advanced generalized muscle weakness and prominent bulbar symptoms (IIB, 9 patients; III, 5 patients; IV, 1 patient). A majority of patients were being treated with anticholinergic agents (46/52, 88%). Nineteen patients (37%) were receiving steroids, and 12 patients (23%) underwent plasmapheresis preoperatively.

Preoperative Evaluation

All patients underwent complete neurological assessment including an edrophonium stimulation test and electromyography. Acetylcholine receptor antibody titers were measured in 44 patients and were elevated in 33 (75%). Anti-smooth muscle antibody titers were measured in 40 patients and were elevated in only 6 (15%).

Computed tomography of the mediastinum was performed in 39 patients (75%). Five patients with thymomas had the diagnosis made preoperatively by computed tomographic scan. There were no false negative and 6 false positive computed tomographic scans, giving this diagnostic method a specificity of 82%, but a positive predictive value of only 45%.

Treatment and Operative Results

All patients underwent median sternotomy for thymectomy. Thymus and mediastinal fat was resected from the diaphragm cephalad to the cervical thymic extensions. Laterally the margins of resection extended to the phrenic nerves and included the mediastinal pleura. The phrenic nerves were not completely dissected.

There was one postoperative death from respiratory insufficiency and sepsis in a patient with acute fulminating myasthenia gravis (Osserman stage III). There were four late deaths (8%) occurring from 6 months to 9 years after thymectomy. All of these late deaths resulted from unrelated disease, although 3 of these patients had active but controlled myasthenia gravis. Postoperative morbidity occurred in 8 patients (15%) and included pulmonary insufficiency (10%), pneumonia (4%), and sternal wound infection (2%). Morbidity was 27% in preoperative Osserman stages IIB, III, and IV versus 11% in Osserman stages I and IIA, but this was not statistically significant ($p > 0.10$).

Pathology

The histology of the resected thymus glands consisted of thymic hyperplasia in 26 patients, thymic atrophy in 11, normal thymus in 8, and thymoma in 7. Five patients with thymomas (71%) improved postoperatively. The response rate of these patients was similar to that of the series as a whole. The 26 patients with thymic hyperplasia (50% of the series) demonstrated a response rate of 72%, significantly better than the 37% response rate seen in the 19 patients (36%) with normal or atrophic thymus ($p < 0.05$). Comparison of histology with preoperative Osserman stage revealed no statistically significant relationship, although there was a trend toward a higher incidence of thymic hyperplasia in the advanced Osserman stages. Twenty-seven percent of specimens from Osserman stage I were thymic hyperplasia, compared with 54% from Osserman stage IIA and 67% from stages IIB, III, and IV.

Preoperative Osserman Stage

The effect of preoperative Osserman stage on clinical outcome is illustrated in Figure 2. Fifteen patients (29%) were in preoperative Osserman stages IIB, III, and IV. Five of these patients (33%) were in complete remission and an additional 8 (53%) were improved at follow-up. There were 26 patients (50%) in Osserman stage IIA preoperatively with 7 in remission (28%) and 9 improved (36%). In contrast, of the 11 patients (21%) in preoperative Osserman stage I, only 2 (18%) were in remission and 1 (9%) improved. Patients in Osserman stages IIA, IIB, III, and IV responded significantly better to thymectomy than patients with ocular symptoms only ($p < 0.01$). Additionally, response to thymectomy improved significantly with increasing preoperative Osserman stage.

Comment

Thymectomy has been accepted as a therapeutic alternative for patients with myasthenia gravis. However, con-

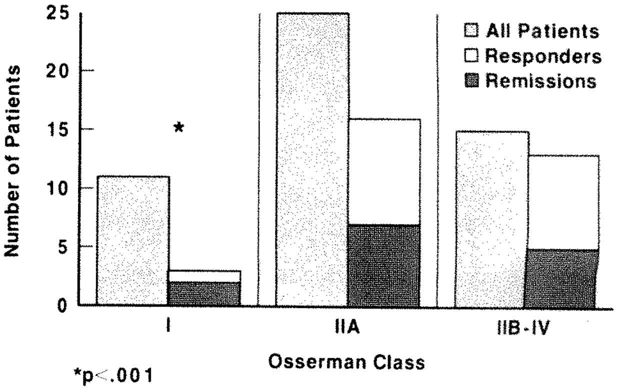

Fig 2. Preoperative Osserman stage versus clinical response (patients in remission or improved) after thymectomy.

troversy persists with regard to the selection of patients, the optimal surgical approach (cervical versus transsternal), and the extent of resection necessary. Comparisons between published series of patients becomes difficult due to differences in surgical philosophy and selection of patients [3, 4]. These difficulties are compounded by the absence of a standardized method for assessing patient status both before and after thymectomy.

Our standard surgical approach involves a median sternotomy and complete resection of the thymus including the cervical extensions. Resection of all anterior mediastinal fat is also advocated. In 72% of patients this fat contains thymic remnants [5]. The phrenic nerves are not extensively dissected to avoid postoperative respiratory compromise.

Transcervical thymectomy may result in incomplete resection. Transsternal reoperative rates to excise unresected thymic remnants as high as 27% have been reported [6]. Cooper and colleagues [4] have described a transcervical approach to thymectomy using a sternal elevator that permits extensive resection. Their reported clinical results are comparable with those obtained with transsternal thymectomy [3]. The transcervical approach confers the potential advantage of a shorter hospital stay. However, it is difficult to objectively compare the two surgical techniques in the absence of a prospective randomized trial.

Our clinical experience encompasses the entire spectrum of myasthenia gravis from minor ocular involvement to acute life-threatening disease. All patients were managed in a standardized fashion.

Data from our series indicate that female patients can expect a significantly better result with thymectomy than males [7]. Patients with thymic hyperplasia also respond better than those with normal or atrophic thymus [8].

Patients with more severe symptoms of myasthenia gravis clearly benefit from thymectomy. In this group of patients thymectomy should be performed early in the course of the disease, with medical therapy being optimized perioperatively to minimize operative morbidity. Plasmapheresis may be useful as adjuvant therapy in patients with impaired respiratory mechanics [9].

Patients with ocular myasthenia (Osserman stage I) demonstrated significantly lower response rates than those patients with more severe disease (Osserman stages IIA, IIB, III, and IV). The response rate of 27% in this small group of patients does not differ significantly from the spontaneous improvement expected from the natural history of the disease as defined by Grob and associates [10].

Our results suggest that transsternal radical thymectomy is a reliable therapeutic alternative with low perioperative morbidity for patients with myasthenia gravis. The best results are to be expected in patients with moderate to severe symptoms. Patients with ocular symptoms only should be managed medically, as the majority of these patients do not improve with thymectomy.

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Intralobar Sequestration
A Missed Diagnosis

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Intralobar pulmonary sequestration is an uncommon but distinct clinical entity that may be the unrecognized cause of recurrent pulmonary infections. Between 1967 and 1987, 10 patients, ranging in age from 5 to 39 years, were found to have an intralobar sequestration. Nine patients (90%) had a history of recurrent pulmonary infections, chronic cough, and intermittent fevers. One patient was asymptomatic. Many patients had been treated with antibiotics on numerous occasions. The delay in diagnosis varied between 3 months and 7 years (mean delay, 1.5 years). The chest roentgenogram was abnormal in all patients. The intralobar sequestration was present in the left lower lobe in 7 patients and the right lower lobe in 3 patients. Bronchography was abnormal in 4 patients in whom it was done. Bronchoscopy was performed in 7 patients, but it was only helpful in excluding other diagnoses. Preoperative thoracic arteriography in 9 patients visualized the systemic arterial supply from the thoracic or abdominal aorta to the intralobar sequestration and helped prevent any catastrophic surgical bleeding. A lobectomy was performed in 9 patients and a segmentectomy in 1 patient without morbidity or mortality. In patients with recurrent infections in the same lower lobe, a high index of suspicion for an intralobar sequestration should prompt early diagnostic arteriography and, if confirmed, early operative intervention.

(Ann Thorac Surg 1989;47:841–7)

Intralobar pulmonary sequestration is an uncommon but distinct clinical entity that may be the unrecognized cause of recurrent pulmonary infections. The term *sequestration,* derived from the Latin verb *sequestrare,* "to separate," was coined by Pryce in 1946 [1] after his clear description established intralobar sequestration as a distinct clinical entity. Generally regarded to result from disturbed embryogenesis, a sequestration is encountered in 1% to 2% of all pulmonary resections [2]. This malformation is characterized by cystic nonfunctioning lung tissue that usually has no communication with the normal bronchial tree and that receives its blood supply from an anomalous systemic artery. The sequestration consists of normal lung elements in an abnormal and disorderly arrangement with variable cartilage, bronchial glands, and alveolar parenchyma. One or more mucus-filled cysts result from mucous secretion into dilated, obstructed bronchioles and alveoli, causing compression aletectasis of surrounding parenchyma (Fig 1). Microscopic communications with adjacent normal lung allow air and, sometimes, bacteria to enter the cysts. If infection is superimposed, the cysts may contain purulent material. In the usual case there is extensive acute and chronic organizing inflammation, usually so severe that little normal tissue remains. Occasionally there is only a single large cyst or a noncystic mass containing branching bronchi that run in the direction of the aberrent artery. Apparently it takes years for these changes to occur, because the disease only rarely becomes apparent in early infancy.

Two types of pulmonary sequestration exist: an intralobar sequestration, in which the abnormal tissue is partly surrounded by normal lung and contained within the visceral pleura, and less commonly, an extralobar type, in which the abnormal lung tissue has its own distinct pleural investment and maintains complete anatomical and physiological separation from the adjacent normal lung.

Several theories have attempted in the past to explain the embryology of pulmonary sequestration [1, 3]. However, they failed to offer a common pathogenesis to the multitude of different clinical presentations. The presence of communications between the intestinal tract and sequestrations led Gerle and associates [4] to the development of a unified theory of formation of intralobar and extralobar sequestrations. This theory, supported by the pathohistological studies of Iwai and co-workers [5], proposes that an additional or accessory lung bud develops in the early embryo from the ventral aspect of the primitive foregut distal to the site of formation of the normal lung bud. The accessory lung bud migrates caudad with the normally developing lung and receives its blood supply from the embryonic splanchnic plexus, which has numerous connections to the primitive dorsal aorta. The vascular connections to the dorsal aorta persist and form the anomalous arterial supply of the developing pulmonary sequestration.

The time at which the accessory lung bud develops in the embryo determines whether the resulting malformation will be intralobar or extralobar. The fact that only a few sequestrations maintain a patent connection with the

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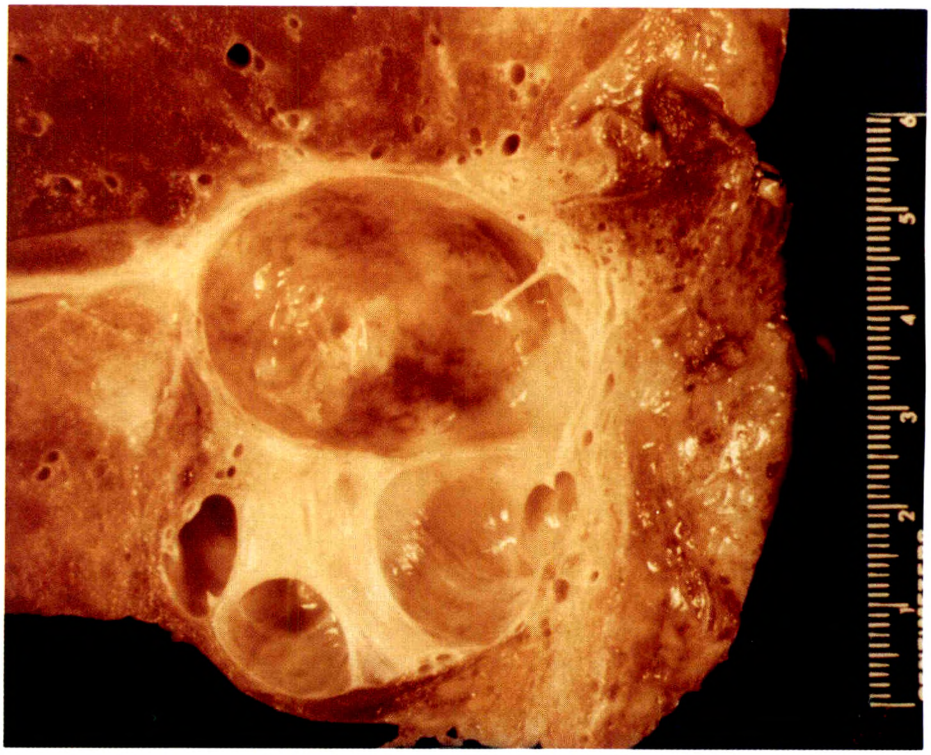

Fig 1. An intralobar sequestration is a multicystic mass of nonfunctioning lung tissue that is partly surrounded by normal lung and contained within the visceral pleura. Mucous secretion in obstructed bronchioles and alveolae results in multiple cysts, which compress surrounding lung, causing atelectasis.

esophagus or stomach may be explained by inadequate blood supply to the communication resulting in its involution [4]. Simultaneously occurring intralobar and extralobar pulmonary sequestrations in which the lesions were noted to be communicating with the gastrointestinal tract strongly support the common origin theory [6]. Albrechtsen [7] reported on a patient with an extralobar pulmonary sequestration connected by a narrow lung tissue pedicle to the left lower lobe. This case represents a definite intermediate link between intralobar and extralobar sequestration, suggesting these lesions are intimately related in etiology and pathogenesis. With regard to the multitude of anatomical variations, intralobar and extralobar sequestrations represent part of a spectrum of malformations, designated "bronchopulmonary-foregut malformations" by Gerle and associates [4]. At one end of the spectrum is an anomalous arterial supply to normal lung. At the other end of the spectrum is abnormal pulmonary tissue but without anomalous arterial supply; namely, bronchogenic cyst, lobar emphysema, and adenomatoid malformation. Between these two extremes lie the variants of sequestration. Recently Rodgers and co-workers [8] have suggested that the term *bronchopulmonary-foregut malformation* is best reserved for those abnormalities of ventral foregut budding directly involving the pulmonary parenchyma and originating from either the tracheobronchial tree or the gastrointestinal tract, such as bronchogenic cysts, sequestrations, and tracheal lobes. They did not include lobar emphysema and cystic adenomatoid malformations, which involve local aberrations of parenchymal development.

The presenting complaint in the majority of patients harboring a sequestration is either repeated localized pulmonary infections or an asymptomatic intrathoracic mass. Special interest in this malformation first arose in 1940 when Harris and Lewis [9] reported operative injury of an anomalous artery to a lower lobe, resulting in the child's death. Although death due to operative trauma to an anomalous artery has subsequently been reported [2], most studies have shown that pulmonary sequestration can be diagnosed accurately before operation and that surgical resection can usually be carried out safely. This paper summarizes our clinical experience with the diagnosis and management of intralobar sequestration, emphasizing the unfortunate delay in diagnosis often accompanying this malformation.

Material and Methods

Between 1967 and 1987, 10 patients, ranging in age from 5 to 39 years, underwent operation for an intralobar sequestration at West Virginia University. There were 7 male and 3 female patients. Six patients were less than 15 years old at diagnosis. The intralobar sequestration occurred in the left lower lobe in 7 patients and the right lower lobe in 3 patients. One patient had an associated gastric duplication cyst and 1 had a left diaphragmatic eventration.

The presenting complaint in 7 patients was repeated pulmonary infections with a history of intermittent fever, cough, and pleuritic chest pain. One patient had hemoptysis as the predominant symptom, and 1 had recurring left-sided pleuritic chest pain. One asymptomatic sequestration was discovered on a chest roentgenogram obtained after an automobile accident.

The clinical history of each patient was carefully reviewed to determine the duration of symptoms and the medical treatment administered. Four of 9 (44%) symptomatic patients had had symptoms for at least 3 months to

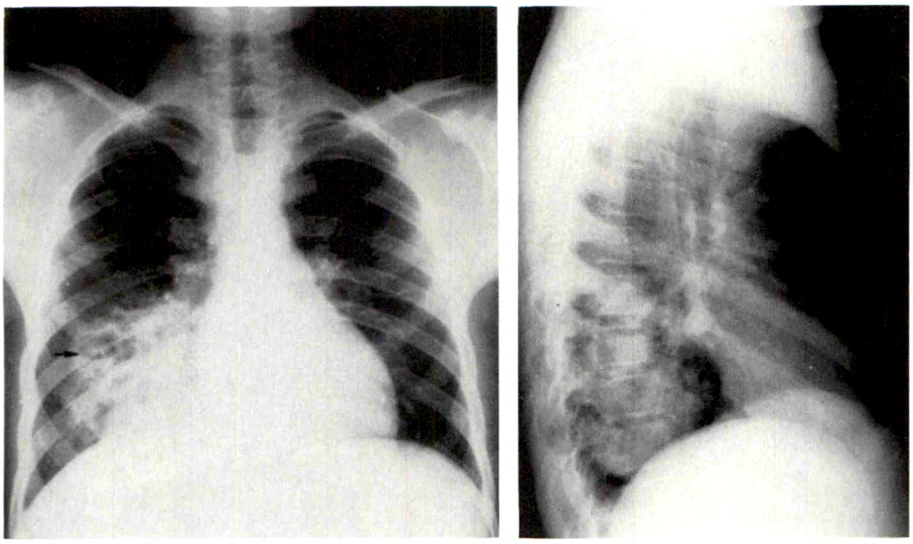

Fig 2. Chest roentgenograms of a right lower lobe intralobar sequestration showing a persistent multicystic appearance in a 15-year-old patient after two courses of antibiotics. Black arrow *points to one of the cysts.*

1 year. An equal number had had symptoms longer than 1 year and up to 7 years. Previous chest roentgenograms had been performed without a diagnosis or suggestion of sequestration in 8 of 9 symptomatic patients. In one patient, the radiologist did suspect sequestration, which led to early referral for further diagnostic studies. Four (44%) symptomatic patients had been treated with multiple courses of antibiotics before referral to the thoracic surgery service for consultation. The antibiotic therapy resulted in transient but incomplete resolution of their symptoms. Their symptoms invariably returned after the antibiotics were discontinued. The diagnosis of sequestration was not suspected in these 4 patients before referral. Persistent pulmonary symptoms and hemoptysis led to earlier referral in the other 5 symptomatic patients.

All 10 patients had abnormal plain chest roentgenograms, suggestive but not diagnostic. Often the film showed evidence of an infiltrate in the posterobasal segment that was indistinguishable from an uncomplicated pneumonia. However, after antibiotic therapy, the opacity cleared and a multicystic lesion with fluid levels remained (Fig 2). Occasionally the initial film showed a single cyst with an air-fluid level (Fig 3). A solid posteromedial lower lobe density was found on incidental chest roentgenogram in 1 asymptomatic patient (Fig 4). Bronchography, performed in 4 patients early in the series, revealed displacement of the terminal bronchioles by a space-occupying lesion. Faint filling of the sequestered segment was noted in 1 patient. Bronchoscopy, performed in 7 patients, was helpful in excluding foreign bodies or tumor. In 3 patients, purulent secretions were seen coming from the bronchi adjacent to the sequestration.

The first patient in the series was operated on with a presumptive diagnosis of intralobar sequestration without aortography. Definite preoperative diagnosis was established in 9 patients by selective arteriography to demonstrate the aberrant systemic arterial supply to the sequestration. The late levophase of the angiograms was studied to define the venous drainage. Table 1 summarizes the arterial supply to the intralobar sequestrations found at operation. In all patients, the origin of the aberrant artery from the abdominal aorta or descending aorta could be delineated by aortography (Fig 5). The presence of multiple arteries was suggested in 2 of the 3 patients in whom they were present. Cardiac catheterization in 1 patient confirmed dual arterial supply to a left lower lobe sequestration from the descending aorta and the left pulmonary artery. The venous drainage in all patients was thought to be to the inferior pulmonary vein on levophase angio-

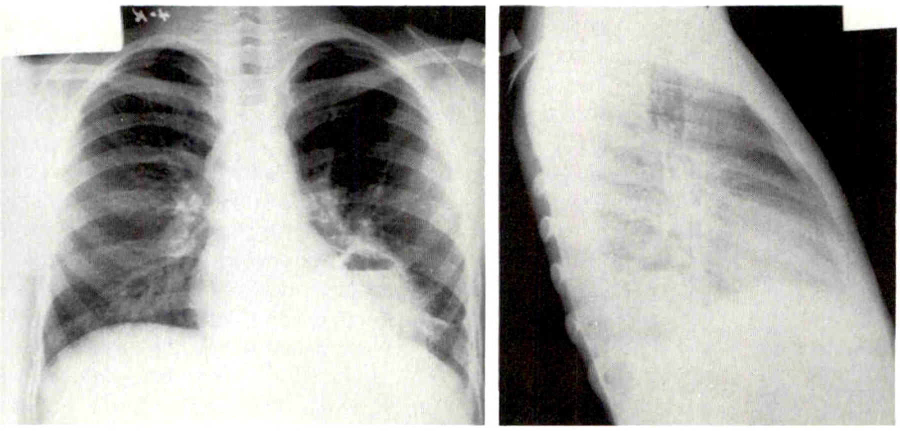

Fig 3. Chest roentgenograms of a left lower lobe intralobar sequestration shows a single cyst with an air-fluid level in an 11-year-old girl during acute infection.

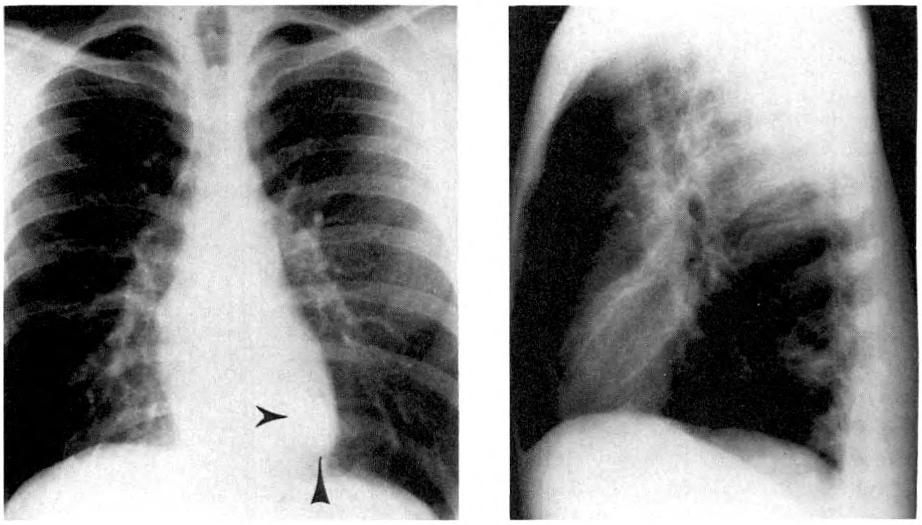

Fig 4. Chest roentgenograms of a left lower lobe intralobar sequestration shows a multilobular solid mass (black arrows) *in an asymptomatic 24-year-old man.*

grams, although at operation one intralobar sequestration was found to drain into the hemiazygos system.

At the time of operation, the aberrant arterial supply to the intralobar sequestration was first carefully defined. The inferior pulmonary ligament was carefully palpated to ascertain if the anomalous artery coursed through it. Multiple arterial branches were carefully searched for. The venous drainage was next determined. The anomalous artery was triply ligated and divided. Some bronchial communication was usually evident between the intralobar sequestration and the rest of the lower lobe because the sequestration inflated when the rest of the lower lobe was hyperinflated. A lobectomy was performed in 9 patients and a basilar segmentectomy in 1 patient. There were no postoperative deaths or episodes of catastrophic hemorrhage. A persistent air leak necessitated prolonged chest tube suction (7 to 20 days) in 2 patients. The patient with a segmentectomy required suction for 20 days. Over long-term follow-up, all patients remain asymptomatic and they have had no further pulmonary infections.

Comment

Though rare, intralobar sequestration is one of the main unrecognized causes of recurrent pneumonia in the pediatric age group. Intralobar sequestrations are encountered about six times as often as the extralobar type, perhaps because the latter is often asymptomatic and consequently unrecognized [2]. Both forms are slightly more common in men than in women. An intralobar sequestration is typically situated in the posterobasal aspect of the lower lobe near the paravertebral gutter, with the left side being involved in about two thirds of the cases [10]. The ten intralobar sequestrations in this series were all confined to the lower lobes, seven in the left lower lobe and three in the right lower lobe. Parke [11] believed that the posterobasal segment, which can be supplied by systemic arteries through the inferior pulmonary ligament, is virtually the only area of lung that could survive without a pulmonary arterial supply. Involvement of the upper or middle lobe occurs very infrequently [12].

Table 1. Arterial Supply in Intralobar Sequestration

Arterial Supply	No. of Patients
Single—descending aorta	5
Multiple—descending aorta	2
Descending aorta, pulmonary artery	1
Single—abdominal aorta	1
Multiple—abdominal aorta	1

The aberrant artery arose from the descending aorta in 8 patients (80%).

Complex multisystem congenital anomalies are frequently associated with extralobar sequestration but rarely with the intralobar type. Although diaphragmatic hernia or eventration is a common associated defect with extralobar types, it can occur with intralobar types [2], as was seen in 1 of our patients. Considering the unified theory of bronchopulmonary-foregut malformations of Gerle and associates [4], anomalies of foregut differentiation such as ectopic pancreatic or hepatic tissue, duplication cysts, or fistulous communications would not be an unexpected finding with intralobar sequestrations [12]. One patient in our series had a gastric duplication cyst that did not communicate with the intralobar sequestration.

An intralobar sequestration usually becomes manifest clinically in the first two decades of life. Turk and Lindskog [10] found that more than 50% of their patients with sequestrations were seen before the age of 20 years. Sixty percent of our patients were seen before 20 years of age. This condition is rare in patients over 40 years of age, although isolated cases have been reported in people in their sixth or seventh decades. The onset of symptoms is usually many months before diagnosis, as noted in this series. Nine patients had a history of prior respiratory infections, dating back 3 months to 7 years (mean, 1.5 years). The broad spectrum of clinical symptoms is determined by the various anatomical relationships. As many as 15% of patients with an intralobar sequestration may be asymptomatic [2]. In such a case the intralobar lesion may be discovered on incidental chest roentgenograms, as was the case in 1 of our patients. A uniformly dense, nonaer-

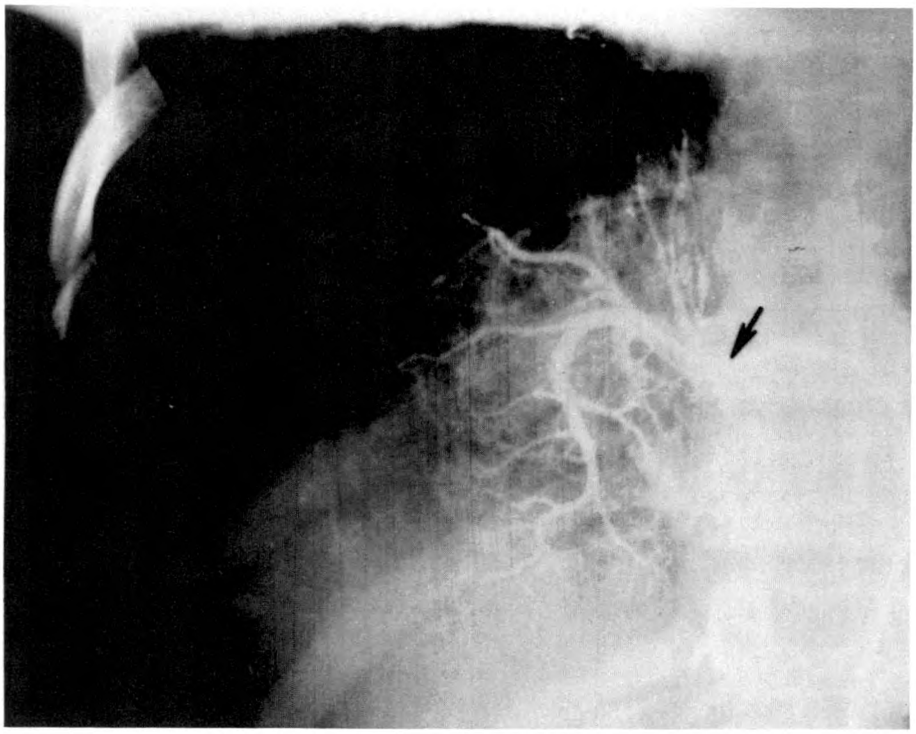

*Fig 5. Selective arteriogram demonstrates a single aberrent systemic artery (*black arrow*) from the descending aorta supplying a right lower lobe intralobar sequestration.*

ated intralobar sequestration in the lower lobe may be confused with a bronchogenic cyst, Bochdalek hernia, or a mediastinal or pulmonary neoplasm.

Blood flow through a sequestered lobe might adversely affect a patient's cardiac output. Solit and colleagues [13] reported reduction of a high cardiac index (4.24 L/min/m^2) to a normal level of 2.89 L/min/m^2 after resection of a sequestered right lower lobe. Their patient experienced a marked improvement in exercise tolerance after resection of the sequestration. Occasionally an intralobar sequestration will be seen in the neonatal period with congestive heart failure and pulmonary edema secondary to a large left-to-left shunt from the aberrent artery through the sequestration into the pulmonary venous system. None of our patients had any cardiovascular symptoms, although several felt that their exercise tolerance was much better after resection.

The most common clinical presentation of an intralobar lesion is recurrent or chronic localized pulmonary infection. Recurrent fever, chills, cough, pleuritic pain, and purulent sputum production are the most common signs. Hemoptysis, noted in 1 of our patients, is not an unexpected symptom, considering the abundant blood supply to the sequestered segment. Classically the bronchial system in an intralobar sequestration does not communicate with the normal bronchial tree. However, secretion of mucus within an intralobar sequestration causes a cystic swelling with subsequent compression atelectasis of the surrounding normal lung tissue. Superimposed infection then spreads easily to the sequestration, reestablishing bronchial communication and thus producing the typical clinical picture associated with intralobar sequestration. Hematogenous spread of infection to the sequestration could lead to similar pathological changes. The chest roentgenogram usually shows a single large cyst with an air-fluid level or a multicystic lesion. Intralobar sequestration can be confused with pneumatoceles, pneumonia, bronchiectasis, or lung abscess, and consequently operation is often delayed. Secondary infection of these cystic lesions is an almost constant feature. Complete resolution of the pulmonary process is difficult because of inadequate bronchial drainage. Extension of the inflammatory process to the pleural cavity may result in the development of an empyema. If the sequestration communicates with the esophagus or stomach, patients may have gastrointestinal symptoms of dysphagia, regurgitation, vomiting, or hematemesis [4, 12].

The chest roentgenograms in all our patients were distinctly abnormal, but the possibility of an intralobar sequestration was rarely initially suspected. The delay in diagnosis occurred before referral to the thoracic surgery service. Review of the clinical histories of the 9 symptomatic patients suggests a lack of appreciation of the classic chest roentgenographic findings on the part of the local physician or radiologist. Once seen by the thoracic surgery service, the diagnosis was promptly made. An indolent process in the posterobasal segment of the lower lobe in a young person with recurrent localized pulmonary infections should suggest the possibility of an intralobar sequestration.

Bronchography usually only shows displacement of terminal bronchi by the sequestration, as noted in 4 of our patients. Filling of the sequestered segment with contrast material seen in 1 of our patients is uncommon, even when air-fluid levels are present within the cysts. Zelefsky and colleagues [14] reported 6 cases in which the contrast medium entered the cystic area, suggesting the confusing diagnosis of cystic bronchiectasis. Bronchoscopy may be helpful in excluding other diagnoses. Tomography can demonstrate the absence of bronchi entering a sequestration, but rarely visualizes the aberrant arteries. Barium esophagogram is indicated in patients with gastrointestinal symptoms, and it may also warn the surgeon of an abnormal fistulous communication with the gastrointestinal tract.

With an appropriate index of suspicion, the most definitive technique of establishing the diagnosis of intralobar sequestration is selective arteriography to demonstrate the aberrant arterial supply to the sequestration and the venous drainage of the sequestration and the ipsilateral lung. Arteriography was first used by Kenney and Eyler [15] to establish the site of the anomalous blood supply. Single or multiple aberrant arteries, usually from the descending aorta just above the diaphragm, ascend in the inferior pulmonary ligament to enter the sequestration. In 10% to 15% of patients, branches from the abdominal aorta pierce the diaphragm to supply the sequestration [2]. Two (20%) patients in this series had an aberrant artery from the supraceliac abdominal aorta. Subdiaphragmatic origin of aberrant arteries is more common in right-sided lesions [16]. The arterial supply is usually a single vessel that is disproportionately large, measuring 0.5 to 2.0 cm in diameter. If the artery is 3 mm or less in diameter, it is likely to be one of multiple vessels, occurring in 15% of cases [10]. Multiple aberrant arteries were seen in 3 (30%) of our patients. Dual arterial supply from both the descending aorta and pulmonary artery, as seen in 1 of our patients, has been infrequently reported [3].

The venous drainage from intralobar sequestration is almost always to the inferior pulmonary vein, establishing a systemic arterial-to-left atrial shunt. This left-to-left shunt occurs in no other well-recognized clinical entity. Occasionally, drainage is solely to the azygos or hemiazygos system, and rarely it is to an intercostal or innominate vein [12]. Dual venous drainage to both pulmonary and systemic veins is most uncommon [3, 10]. In a recent series, 60% of right-sided intralobar sequestrations had an abnormal venous return compatible with the scimitar syndrome [17]. The importance of preoperative assessment of the venous drainage as well as the aberrant arterial supply is underlined by occasional reports of postoperative fatalities due to ligation of anomalous veins that constituted the sole or major route of drainage of the entire ipsilateral lung [18].

Some authors have questioned the need for preoperative angiography; however, preoperative localization of the hazardous aberrant arteries affords a safer operative approach [10]. Arteriography also is helpful in differentiating this lesion from other abnormalities of the lung, such as pulmonary arteriovenous fistulas. However, demonstration of a systemic artery supplying lung tissue is not pathognomonic of sequestration. Arteriography must be interpreted in concert with the clinical presentation and the chest roentgenograms.

Recently several investigators have utilized ultrasound, computer assisted tomography, and magnetic resonance imaging to diagnose sequestration and the aberrant arterial supply [19–21]. As a sequestration may appear as a solid, homogeneously echogenic mass on ultrasound, differentiation from an adenomatoid malformation may be difficult. Although a range of findings in sequestrations have been reported using computer assisted tomography, including calcification, intraabdominal localization, association with gastric duplication, bilaterality, and aberrant arterial supply, computer assisted tomography may be at a disadvantage (a) when there are multiple feeding vessels; (b) if anomalous vessels are extremely tortuous or have an oblique orientation, especially when they arise from the abdominal aorta; and (c) in the pediatric age group, in which the resolution of all but the fastest scanners may be inadequate to provide sufficient anatomical detail.

The use of magnetic resonance imaging also has serious limitations in identification of congenital pulmonary anomalies. Alterations in the parenchymal architecture of the lung and the intrapulmonary vascularity are sometimes difficult to appreciate. Although large anomalous vessels may be recognized, smaller anomalous vessels may not be detected. This may prove a limitation in potential surgical cases, for which detailed angiographic anatomy is highly desirable. Still, the most important element in the diagnosis is a high index of suspicion of encountering the lesion. Increasing the awareness of primary care physicians of the clinical manifestations of intralobar sequestration should lead to more prompt recognition and treatment of this condition.

Because reinfection is inevitable in a poorly drained sequestered segment, pulmonary resection in a quiescent phase after treatment of intercurrent infection is the only rational treatment. The ideal method of treatment would be removal of the lesion itself by segmentectomy, and this is advocated by some. However, the procedure rarely is feasible because of chronic intralobar infection with obliteration of segmental planes. Early diagnosis may permit less extensive resections. Only 1 patient in this series had a segmentectomy; this patient had a prolonged air leak. Segmental resection carries a high complication rate in some series, with prolonged air leak and recurrent infection occasionally requiring reoperation for completion lobectomy [22]. For this reason it is our belief that lobectomy is the operation of choice. Children tolerate lobectomy extremely well, with growth and expansion of the remaining lung tissue so that total lung volume and pulmonary function return toward normal [23].

The chief technical hazard at operation is inadvertent transection of the anomalous systemic artery. The friable anomalous artery may be quite large with intimal thickening and premature arteriosclerotic changes [2]. Histologically, the artery is usually elastic rather than muscular, thus resembling a pulmonary artery and making surgical handling of this vessel quite precarious. It may be necessary to isolate the aorta above and below the origin of the vessel to obtain optimum control. Once severed, the artery may retract into the mediastinum or below the diaphragm. Several reports have described fatal intraoperative hemorrhage during pulmonary resection when sequestration was unsuspected [9]. It should be the habit of every thoracic surgeon to palpate the inferior pulmonary ligament before any pulmonary resection because anomalous arteries may arise in this structure even without sequestration. In patients with a right-sided intralobar sequestration and scimitar syndrome, the pulmonary venous drainage should be carefully assessed to avoid severe complications connected with resection of the sequestration alone without repair of the scimitar syndrome. The unusual gastrointestinal connections that can be associated with sequestration must also be kept in mind.

Even in asymptomatic intralobar sequestration, most authors recommend prophylactic excision [12], as there is likelihood of infection as well as danger of hemorrhage caused by arteriovenous anastomoses. In the rare cases of bilateral intralobar sequestrations, the symptomatic lesion should be resected first; some authors then recommend subsequent resection of the asymptomatic lesion [24]. Even in the presence of the most discrete radiological signs, pathological examination may reveal a florid inflammatory process. Furthermore, the occurrence of fungal infections, tuberculosis, and even tumors within sequestered areas has been reported [24, 25]. However, Zumbro and associates [26] maintain that observation rather than operation might be considered in asymptomatic patients with an arteriographically proven intralobar sequestration that contains no air-filled cysts. Removing an asymptomatic sequestration may prevent infection and destruction of surrounding normal lung tissue, resulting in a more extensive resection.

Simple ligation of the systemic artery to the sequestration may rarely be indicated for correction of a hemodynamically significant shunt in a critically ill infant with congestive heart failure [27]. Ligation of the anomalous artery may cure the heart failure and prevent subsequent hemoptysis, but it probably will not prevent later infection, the most common cause of morbidity in intralobar sequestration. On the contrary, devascularization can result in devitalized lung tissue, predisposing the patient to infection.

Intralobar sequestration is challenging and gratifying to diagnose and treat. The diagnosis should always be considered in a child who is seen with repeated localized respiratory infections, particularly in the posterobasal segment of the lower lobes. A lower lobe abscess poorly responding to conventional treatment should strongly suggest the possibility of this congenital lesion. Although chest roentgenograms are usually highly suggestive, selective arteriography is the best technique to accurately diagnose an intralobar sequestration, which presents considerable operative hazard if the surgeon is unaware of the aberrant blood supply. As almost all patients with sequestration eventually require operation, early operation eliminates the risk of potentially life-threatening infections, abolishes the left-to-left shunt through the sequestration, and hastens the return of normal pulmonary function. The results of operation are excellent if special attention is given to the anomalous arterial supply. There were no postoperative deaths and little postoperative morbidity in this series. Prognosis is excellent after resection and long-term follow-up suggests that these patients continue to do well.

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Postoperative Preservation of Pulmonary Function in Patients With Chronic Empyema Thoracis: A One-Stage Operation

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Twenty-two patients with chronic empyema thoracis underwent decortication. In 11 of them, simple decortication achieved sufficient reexpansion of the lung. In the other 11 patients, our new method was indicated because the pleural space was not closed completely by simple decortication. In our procedure, the parietal wall is collapsed, without rib resection, to contact the surface of the decorticated lung. All 11 patients had a one-stage cure. Two of these 11 patients had bronchopleural fistula. The preoperative and postoperative percentage of vital capacity, percentage of forced expiratory volume in 1 second, arterial oxygen tension, alveolar-arterial oxygen pressure difference, and xenon 133 radiospirometry revealed that pulmonary function was well preserved in patients treated by our method as well as in those undergoing simple decortication. The alveolar-arterial oxygen pressure difference during oxygen inhalation improved significantly ($p < 0.05$) after operation compared with the preoperative values in both groups. From the pulmonary function studies, we conclude that our method achieves results comparable with those of simple decortication for the treatment of chronic empyema thoracis. Our procedure is indicated in patients for whom it is thought simple decortication will not lead to primary cure of empyema.

(Ann Thorac Surg 1989;47:848–52)

The object of surgical treatment of empyema thoracis is to remove the pyogenic membrane and obliterate the dead space in the thoracic cavity. No other surgical procedure is needed if decortication results in complete elimination of the dead space by sufficient inflation of the lung. However, additional surgical procedures, such as thoracoplasty or muscle flap plombage, are often needed to achieve complete cure [1, 2]. These procedures result in impairment of pulmonary function because of postural deformity [3–5].

After a comprehensive review of the results of such procedures for empyema thoracis, we [6] developed a new one-stage method. It is indicated for patients with empyema thoracis when simple decortication is not sufficient to reexpand the lung. In this method, the parietal wall, consisting of the parietal pleura, periosteum, and intercostal muscle, is collapsed to contact the surface of the decorticated lung. After the operation, the fluid that collects in the extraperiosteal space collapses the dead space; pulmonary reexpansion is attained later on reabsorption of this fluid. There is no deformity of the thorax postoperatively. Therefore, this procedure is regarded as "extraperiosteal fluid plombage thoracoplasty."

We designed the present study to evaluate preoperative and postoperative pulmonary function in patients undergoing either simple decortication or our new procedure.

Material and Methods

Twenty-two of 34 patients operated on for chronic tuberculous empyema thoracis between March 1978 and October 1980 were studied. These patients were informed about the preoperative and postoperative studies and consented to them. Sixteen patients were male and 6, female. Mean age was 51.0 ± 15.6 years. All patients demonstrated symptoms such as bloody and purulent sputum, chest pain, fever, or dyspnea.

Genesis of empyema, duration of pleural disease, symptoms, and performance status, rated according to the classification of Hugh-Jones [7], were carefully determined in an interview with one of us (K.S.). All patients had a previous history of pulmonary tuberculosis, and 4 had been treated by artificial pneumothorax. The caseous necrosis typical in patients with tuberculosis was observed in all our patients. The lesion was on the left side in 10 patients (5 in the simple decortication group and 5 in the group having operation by our method) and on the right side in 12 patients (6 in each group).

In this study, total empyema was defined as extension of the empyemic space from the pulmonary apex to the diaphragm as observed on the chest roentgenogram. When the radiological findings were otherwise, the empyema was considered partial. There were 7 patients with total empyema, and our new procedure was indicated in 6 of them.

All patients received closed-chest tube drainage to irrigate the thoracic cavity for a few weeks with a saline

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solution containing antibiotics. Afterward, decortication was the treatment of choice.

In 11 patients sufficient pulmonary reexpansion was attained by simple decortication. The mean age of this group was 52.6 ± 12.0 years. Among the other 11 patients, 9 had insufficient closure of the pleural space, and 2 had the complication of bronchopleural fistula. Our method was indicated for these 11 patients. The mean age of this group was 54.6 ± 12.6 years.

Details of our procedure have been described [6]. Briefly, this is a surgical procedure in which the bony thorax is left intact, but the intercostal muscle and the rib bed are separated subperiosteally over a wide area to adhere to the visceral pleura. The fluid collecting above the parietal sheath (consisting of the parietal pleura, periosteum, and intercostal muscle) presses the intercostal muscle flap adequately against the decorticated lung and closes the intrathoracic dead space. In time, as the adhesion becomes complete, reexpansion of the lung is promoted by reabsorption of the fluid in the periosteal space.

The operation was successful in all patients. Five to 6 months after operation, the symptoms due to infection or fistula had disappeared, and appropriate lung inflation was observed on the chest roentgenogram (Fig 1).

Pulmonary Function Studies

Pulmonary function studies were performed both before operation and an average of 6 months postoperatively (6.1 ± 1.4 months [mean ± standard deviation]).

OVERALL PULMONARY FUNCTION STUDY. Using a respirometer, the vital capacity (VC) and forced expiratory volume in 1 second (FEV_1) were measured. The %VC and $\%FEV_1$, ie, the percentage of the predicted normal values, were then calculated.

The expired air of patients who had lain on their backs quietly for 20 minutes was collected for the subsequent 10 minutes in a Douglas bag. The fraction of expired carbon dioxide ($FEco_2$) was measured by thermal conductivity, and the fraction of expired oxygen (FEo_2) was determined with a magnetic oximeter.

At the same time, arterial oxygen tension (PaO_2) and arterial carbon dioxide tension ($PaCO_2$) were measured. From these values, the alveolar-arterial oxygen pressure difference ($P[A\text{-}a]O_2$) was calculated for all patients as follows: partial pressure of alveolar oxygen (PAO_2) = $0.21\ (760 - 47) - (0.21 - FEo_2)/(FEco_2 \times PaCO_2)$; $P(A\text{-}a)O_2 = PAO_2 - PaO_2$. In some cases, the arterial blood was sampled during inhalation of pure oxygen for more than 20 minutes to measure $P(A\text{-}a)O_2$. The $P(A\text{-}a)O_2$ during pure oxygen inhalation was calculated as $(760 - 47 - PaCO_2) - PaO_2$.

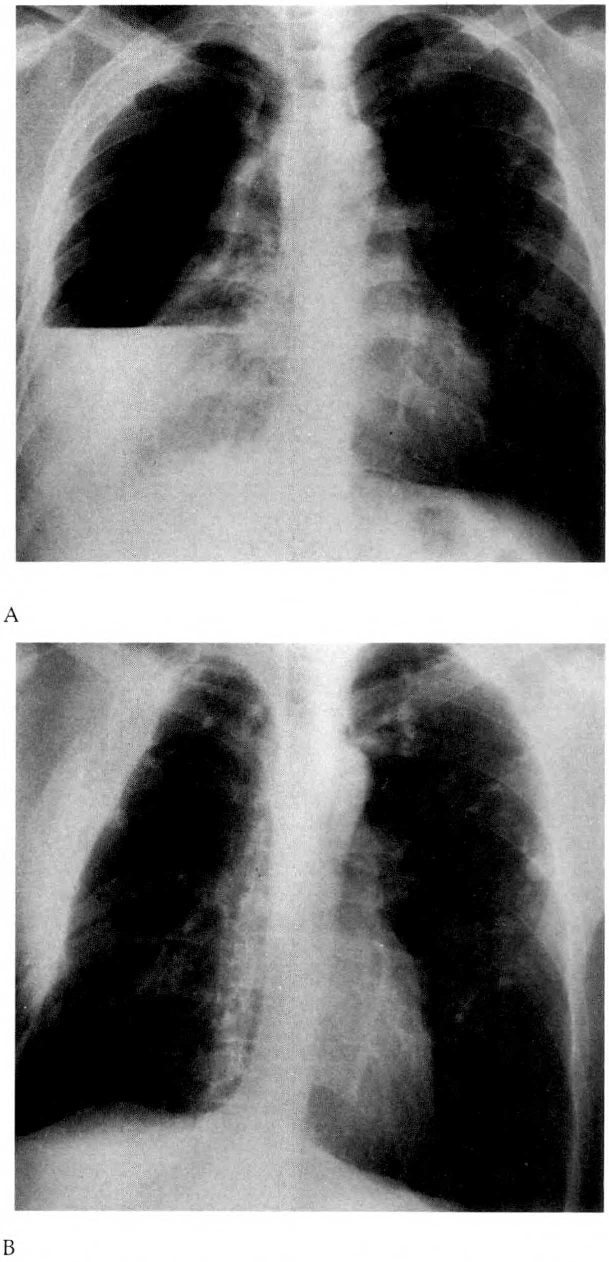

Fig 1. (A) The right lung was completely collapsed because of empyema with bronchopulmonary fistula. The patient underwent operation by our method, and symptoms and signs of empyema disappeared. (B) Chest roentgenogram made 8 years later showed almost complete reinflation of the lung.

RADIOSPIROMETRY. Six scintillation detectors were attached to the patient's back, three detectors on each side. Each detector, which consisted of an NaI crystal (38 × 6 mm) and a photomultiplier, was connected to a six-channel recorder by a pulse-height analyzer and rate meter. The top edges of the upper detectors were set at the level of the clavicle at maximal inspiration, the middle detectors at the level of the sixth thoracic vertebra, and the lower detectors at the level of the tenth thoracic vertebra. Four millicuries of xenon 133–labeled gas and ambient air were introduced into the spirometer; the patient was instructed to inhale the gas from the maximal expiratory level to the maximal inspiratory level and to hold his or her breath for 4 seconds to obtain a regional count rate.

The VCs of the left and right sides were calculated from the overall VC multiplied by the sum of the fractional distribution of the regional count rate on each side. After complete washout of the ^{133}Xe, 2 mCi of ^{133}Xe–labeled

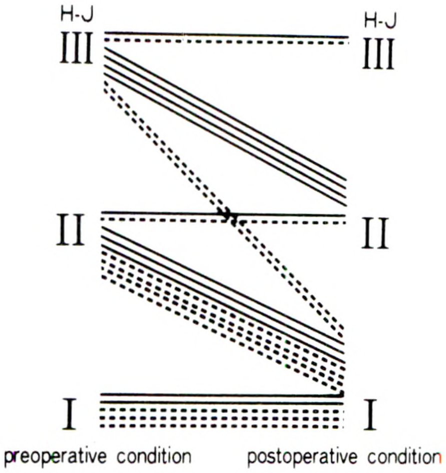

Fig 2. Performance status rated by the Hugh-Jones (H-J) *index [7].* I *= No substantial restriction of normal activities; can keep up with a healthy person of the same age when working and walking.* II *= Independent in essential activities of daily life; dyspnea on climbing stairs or an incline, but not on level walking.* III *= Dyspnea usually occurs during activities such as showering or dressing; not dyspneic at rest; can walk 1,000 m at own pace, but cannot keep up with a healthy person of own age.* Broken lines *indicate patients undergoing simple decortication and* solid lines, *those treated by our method.*

solution was rapidly administered intravenously while the patient held his or her breath at the end-tidal level until each regional count rate reached a plateau on the recorder. The patient was then instructed to inhale air up to the maximal inspiratory level and to hold his or her breath for 4 seconds to record the regional perfusion rate. The percentage distributions of the perfusion counts were totaled for the left and right sides.

Statistical Analysis

Data are expressed as the mean ± one standard deviation. The paired or unpaired *t* test was applied to analyze the statistical difference; a *p* value of less than 0.05 was regarded as significant [8].

Results

Change in Hugh-Jones Criteria After Operation

The performance status as rated by the criteria of Hugh-Jones [7] is demonstrated in Figure 2. In the simple decortication group, the Hugh-Jones index was III in 3 patients, II in 5 patients, and I in 3 patients before operation. The index decreased from III to I in 2 patients and from II to I in 4 patients after operation. In the group undergoing operation by our method, the index was III in 5 patients, II in 4 patients, and I in 2 patients before operation. The index decreased from III to II in 4 patients and from II to I in 3 patients after operation. There were no patients in either group whose condition became worse after operation.

Duration of Pleural Disease and Symptoms

For the 11 patients who attained an acceptable result by simple decortication, the mean duration of the disease was 18.5 ± 16.7 years (range, 4 months to 32 years). For the 11 patients undergoing our procedure, the mean duration was 29.9 ± 11.9 years (range, 3 to 47 years). The difference in duration of disease between the two groups was not significant.

The duration of symptoms averaged 11.9 ± 10.7 months in the simple decortication group and 20.2 ± 10.7 months in the group undergoing our procedure. There was no significant difference in duration of symptoms between the two groups.

Blood Sedimentation Rate

Blood sedimentation rate decreased significantly in the simple decortication group ($p < 0.01$) and in the group having our operation ($p < 0.05$) (Table 1).

Overall Pulmonary Function

The results for overall pulmonary function are summarized in Table 1. The %VC did not change significantly after operation in either group. However, the preoperative and postoperative %VC values were significantly ($p <$

Table 1. Changes in Blood Sedimentation Rate and Overall Lung Function Before and After Operation[a]

Procedure	Blood Sedimentation Rate (mm/h)	%VC	%FEV_1	PaO_2 (mm Hg)	$P(A\text{-}a)O_2$ (mm Hg) Room Air	$P(A\text{-}a)O_2$ (mm Hg) Pure O_2[b]	$PaCO_2$ (mm Hg)
Simple decortication (n = 11)							
Preoperative value	37.3 ± 26.8	66.6 ± 8.4	76.9 ± 10.3	89.0 ± 9.2	17.3 ± 9.1	191.9 ± 32.2	37.7 ± 5.1
Postoperative value	12.1 ± 15.3[c]	71.3 ± 12.5	77.9 ± 6.8	93.4 ± 10.1	12.6 ± 9.6	110.7 ± 34.8[d]	38.2 ± 3.5
Our operation (n = 11)							
Preoperative value	47.3 ± 48.2	54.6 ± 14.5[e]	75.1 ± 11.7	82.1 ± 8.5	19.6 ± 7.4	168.6 ± 33.0	42.5 ± 4.1
Postoperative value	23.7 ± 18.8[d]	55.7 ± 13.1[e]	72.4 ± 12.9	88.7 ± 9.0[d]	13.2 ± 7.6[d]	102.6 ± 42.0[d]	42.1 ± 5.6

[a] Data are shown as the mean ± one standard deviation. [b] Data were obtained from 3 patients in the simple decortication group and 6 patients having operation by our method. [c] Significance: $p < 0.01$, preoperative versus postoperative value. [d] Significance: $p < 0.05$, preoperative versus postoperative values. [e] Significance: $p < 0.05$ between two groups in preoperative or postoperative value.

$P(A\text{-}a)O_2$ = alveolar-arterial oxygen pressure difference; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; %FEV_1 = percentage of predicted normal value for forced expiratory volume in 1 second; %VC = percentage of predicted normal value of vital capacity.

Table 2. Radiospirometry Before and After Operation[a]

		Split %VC		
Procedure	$\dot{V}$%	Affected Side	Unaffected Side	$\dot{Q}$%
Simple decortication (n = 11)				
Preoperative value	23.9 ± 7.9	16.4 ± 6.7	50.1 ± 5.5	25.1 ± 9.5
Postoperative value	29.9 ± 9.0[b]	21.8 ± 8.4[b]	49.3 ± 9.0	31.0 ± 11.0
Our method (n = 11)				
Preoperative value	21.5 ± 13.4	12.8 ± 11.1	41.7 ± 9.3[c]	24.2 ± 14.4
Postoperative value	20.5 ± 11.7	12.0 ± 8.0[c]	43.7 ± 9.9	21.6 ± 12.3

[a] $\dot{V}$% and $\dot{Q}$% are percent distribution of ventilation and perfusion, respectively, on the affected side. Split %VC was calculated from $\dot{V}$% and overall VC (vital capacity), normalized by Baldwin's equation. [b] Significance: $p < 0.05$, preoperative versus postoperative value. [c] Significance: $p < 0.05$ between two groups in preoperative or postoperative value.

0.05) lower in the group having operation by our method, compared with those in the decortication group.

The %FEV_1 did not change significantly in either group.

The PaO_2 and $P(A\text{-}a)O_2$ during inhalation of ambient air improved significantly ($p < 0.01$) in the group treated by our procedure. Although PaO_2 and $P(A\text{-}a)O_2$ improved slightly in the simple decortication group, the change was not significant. The $P(A\text{-}a)O_2$ during inhalation of pure oxygen was measured in 3 patients in the simple decortication group and 6 patients in the group operated on by our method. Significant ($p < 0.01$) improvement was seen after operation.

The $PaCO_2$ was within normal limits and did not show a significant difference after operation in either group.

Radiospirometry

Table 2 demonstrates the changes in split pulmonary function. In the decortication group, the ventilation distribution and %VC on the affected side showed significant ($p < 0.05$) improvement after operation. In the group having operation by our method, however, there was no significant change in either of these variables for the affected side. After operation, the %VC on the involved side in the group operated on by our method was significantly lower ($p < 0.05$) than that in the decortication group.

On the contralateral side, the preoperative %VC in the group having operation by our method was significantly lower ($p < 0.05$) than that in the decortication group. No significant changes in the %VC of the contralateral side were detected after operation in either group. The perfusion distribution on the involved side also was not changed significantly by operation in either group.

Comment

Although the incidence of pulmonary resection for pulmonary tuberculosis has declined remarkably as a result of advances in antituberculosis drug therapy, there are still many patients in Japan with empyema of tuberculous origin. They show symptoms and signs of increased pleural effusion, fever, productive cough, and consequent limitation of performance.

Previously, we [6] performed open drainage by the modified Eloesser operation in 6 patients in whom no improvement in systemic symptoms occurred after chest tube drainage and irrigation with antibiotics. This technique consists of cleansing the empyema cavity for a few months through a large window opened by resecting several ribs, covering the drainage site with gauze pads, and then obliterating the cavity by thoracoplasty and construction of pedicled muscle flaps. These patients showed a change in VC after operation compared with the preoperative value of −3.9% ± 8.3%, which was significantly ($p < 0.001$) lower than the changes in VC after decortication (+8.6% ± 13.6%) and after operation by our method (+6.5% ± 13.2%).

In studying patients who had undergone thoracoplasty for empyema thoracis, Powers and Himmelstein [4] demonstrated that the decrease in VC was greater than 30% in severely scoliotic patients and less than 20% in patients with no or minimal scoliosis. Huang and Lyons [5] found that the development of cardiorespiratory failure in patients undergoing pneumonectomy for tuberculosis correlated significantly ($p < 0.01$) with added thoracoplasty because of the restrictive ventilatory defect, abnormalities in the ventilation/perfusion relationship and diffusing capacity during exercise, and consequent hypercapnia and hypoxemia. Functional disturbance caused by the chest deformity [3, 9] is inevitable after thoracoplasty.

Therefore, since 1978, we have preferentially used our method in patients with chronic empyema thoracis who did not obtain sufficient reexpansion of the collapsed lung by simple decortication. We have used this method successfully even in patients with bronchopleural fistula. The background for this operative procedure was extraperiosteal plombage thoracoplasty, which was extensively used for surgical treatment of pulmonary tuberculosis from 1950 to 1960 [10–12]. In this sense, our method can be regarded as extraperiosteal fluid plombage thoracoplasty.

It is notable that our procedure maintained lung volume at the preoperative value, and was indicated even in patients with compromised lung function. In fact, the preoperative %VC was 38%, 38%, and 34% in 3 patients with total empyema who underwent our procedure. Although they needed a tracheostomy to assist ventilation in the early postoperative management, %VC rose to 43%, 43%, and 36% at 6 months after operation. In these 3 patients, conventional thoracoplasty or panpleuropneumonectomy would have been difficult, as the ventilation distribution on the affected side (11%, 31%, and 15% of the total) would have been partly or completely sacrificed by these procedures.

The results of lung function studies after decortication have demonstrated slight but not significant improvement in VC, total lung capacity, and oxygen consumption [13–17] or perfusion distribution on the affected side [18]. Toomes and associates [19] studied 161 patients who underwent decortication, and concluded that VC, FEV_1, and maximal voluntary ventilation did not show any significant changes.

Benfield and co-workers [20, 21] completely collapsed the left lung in dogs by transecting the bronchus and reexpanded them by reanastomosing the bronchus 9 to 38 weeks later. They demonstrated that a mean pulmonary artery pressure of 13.5 mm Hg at baseline was increased to 31.6 mm Hg by right pulmonary artery occlusion. The animals did not tolerate such occlusion without distress.

Ahmed and Harrison [22] studied the histology of reexpanded rabbit lungs after 28 weeks of collapse, and concluded that fibroelastic thickening of the intima of the pulmonary muscular artery had occurred. This indicates that organic change had taken place in the parenchyma of the chronically collapsed lungs. Therefore, it seems quite natural that %VC and $\%FEV_1$ in our study did not change significantly in either operative group.

The preoperative %VC on the contralateral side was significantly lower in the group operated on by our method than in the decortication group: every patient with a %VC on the unaffected side of greater than 40% underwent simple decortication, and every patient with a %VC on the unaffected side of less than 40% underwent our procedure. These figures are the result of the compression of the contralateral lung tissue or the mediastinal shift caused by the large empyema space in many patients undergoing our procedure. In patients having our procedure, the contralateral %VC improved from 48% to 62% and from 38% to 48% in 2 patients with a remarkable mediastinal shift caused by the total empyema.

In the experiment already described, Long and colleagues [21] demonstrated that the shunt rate decreased from 14% to 1.0%, although ventilation distribution to the reexpanded left lungs was only 24.6% and oxygen consumption per minute was only 13.8% of the total after reexpansion. The contribution to both ventilation and oxygen consumption per minute of the left lung in the control animals was approximately 40% of the total. The cardiac output in the experimental dogs was almost the same as that in the control animals.

Although we did not measure the oxygen tension of the mixed venous blood to calculate shunt rate, the significant changes in PaO_2 and $P(A\text{-}a)O_2$ in the group operated on by our method may have been due to a decrease in the intrapulmonary shunt, as $P(A\text{-}a)O_2$ during oxygen inhalation decreased significantly in 6 patients undergoing our procedure. The fact that simple decortication was performed only in patients with relatively slight impairment of lung function could be responsible for the nonsignificant changes in PaO_2 and $P(A\text{-}a)O_2$, as changes in these variables were within the normal range.

We propose that our method be used for patients with chronic empyema thoracis in whom simple decortication does not achieve sufficient inflation of the collapsed lung and in patients with bronchopleural fistula, not only to prevent pleural inflammation but also to obtain recovery of performance.

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Aneurysms After Patch Graft Aortoplasty for Coarctation of the Aorta: Long-Term Results of Surgical Management

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Twenty-two (32.8%) of 67 patients who had patch graft aortoplasty for aortic coarctation underwent reoperation because of aneurysm formation opposite or at the site of the patch. The mean age at primary repair was 25.3 years (standard deviation, 9.5 years). Reoperation took place 12.3 years (standard deviation, 3.7 years) later. In 19 patients, the aneurysm was resected and the aorta reconstructed with a tubular prosthesis. In 3 patients, the aneurysm was given external support. There were no hospital deaths. Recurrent nerve paralysis (36%) and bleeding necessitating repeat thoracotomy (32%) were the most common complications. Mean follow-up was 4.6 years. No aneurysms developed at the site of reoperation. Two patients died of causes not related to reoperation. Reconstruction with a tubular prosthesis gives good long-term results in patients with aneurysm formation after patch grafting for coarctation. External support offers technical advantages in select patients. Close follow-up of patients who have coarctation repair with a patch graft is essential.

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In the patient with a lengthy coarctation of the aorta, resection and anastomosis may not be possible. A tubular interposition graft can be used. In 1957, Vossschulte [1] described the repair of long coarctations by patch graft aortoplasty only. The method has obvious technical advantages at the time of operation and came into wide use in our hospital as elsewhere [2]. Later, we [3, 4] and others [5–7] became concerned about the number of aneurysms that developed, most opposite the synthetic patch used for repairing the coarctation. The incidence of late aneurysm formation was 27% among patients in whom the synthetic patch technique was used to repair coarctation of the aorta in adulthood [4], and the incidence increased with continued follow-up. We have surgically treated 22 patients with such aneurysms, and report here the long-term results of these reoperations.

Material and Methods

Patch graft aortoplasty with a Dacron or Teflon graft was performed between 1967 and 1978 as the preferred method for repairing aortic coarctation not suitable for direct end-to-end anastomosis. The technique used for coarctation repair was identical to that described by Vossschulte [1, 2, 4]. Our patients ranged in age from 15 to 54 years. Sufficient follow-up data are available on 67 long-term survivors of the primary operation.

By 1988, 22 enlarging aneurysms at the patch coarctation repair site had been detected on serial roentgenograms, computed tomographic scans, aortograms, or a combination of these. The 22 patients with aneurysm formation underwent reoperation between 1978 and 1988, and thereafter were followed closely using the radiological procedures indicated, chiefly serial chest roentgenography. There were 17 male and 5 female patients. The mean age at coarctation repair was 25.3 years (standard deviation, 9.5 years). The aneurysms were small when detected and increased in size slowly over 1 to 3 years. The time between correction of the coarctation with a patch graft and reoperation for aortic aneurysm was 12.3 years (standard deviation, 3.7 years). Examples of the aneurysms are shown in Figures 1 through 3.

Results

The repair in 19 patients included aneurysm resection and replacement of the aortic continuity with a tubular Dacron prosthesis. The technique has been described previously [4], and the operative findings did not differ essentially from those reported. To protect the spinal cord from ischemia, femorofemoral perfusion was employed in 16 patients and left atrium–femoral bypass in 3. In the 3 other patients, close follow-up had revealed that aneurysms that were rather small in diameter at first, had definitely enlarged. These patients were treated by external wrapping of the aneurysm with a Dacron graft.

The 22 operations were performed without hospital deaths. The postoperative complications, which include those from our earlier experience [4], are as follows: recurrent laryngeal nerve paralysis, 8 patients (36%); postoperative hemorrhage (repeat thoracotomy), 7 (32%); pneumonia or atelectasis, 5 (23%); hemiparesis (right-sided), 2 (9%); phrenic nerve paralysis, 1 (5%); and claudication of the left upper limb, 1 (5%).

The average follow-up after reoperation was 4.6 years

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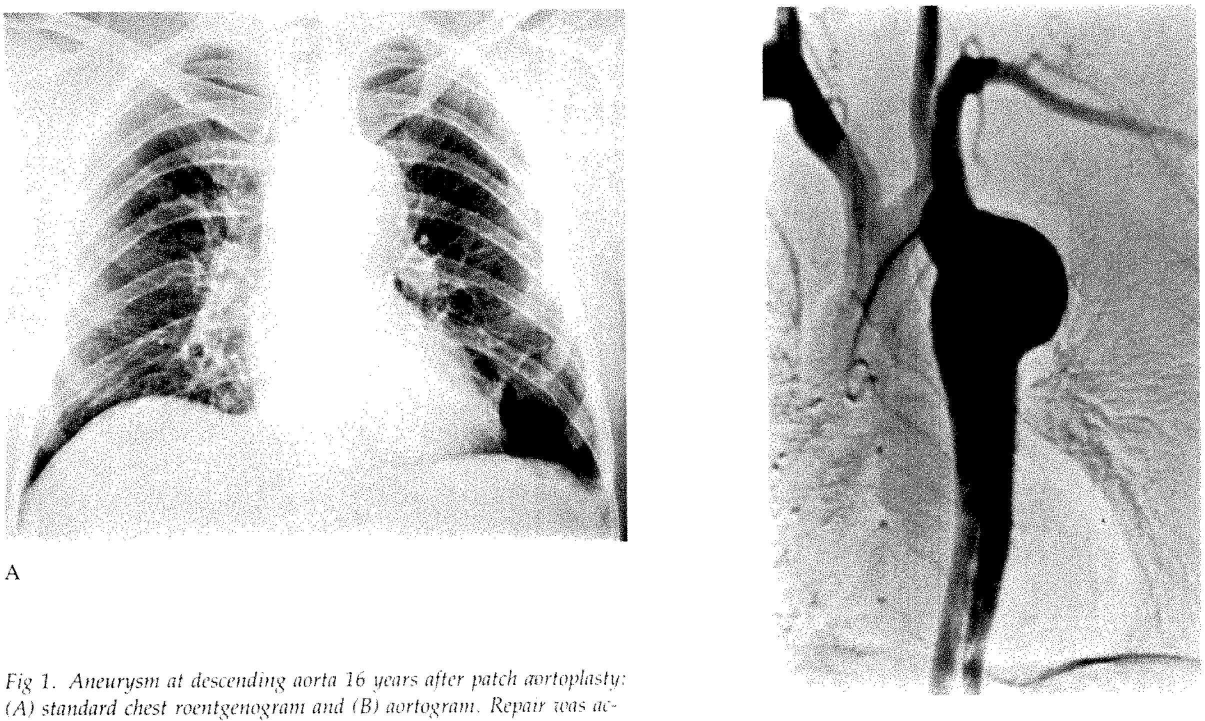

Fig 1. Aneurysm at descending aorta 16 years after patch aortoplasty: (A) standard chest roentgenogram and (B) aortogram. Repair was accomplished using a tubular prosthesis.

(range, 3 months to 10 years). Follow-up included clinical examination with blood pressure measurements and chest roentgenography, complemented by computed tomography or angiography in 5 patients (Fig 4).

Two of the 22 patients died 2 and 6 years after reoperation. The cause of death was not related to aneurysm repair in either patient.

Follow-up did not reveal aneurysm formation in the remaining descending aorta, at suture lines, or at the Dacron prosthesis. A systolic pressure gradient of 40 mm

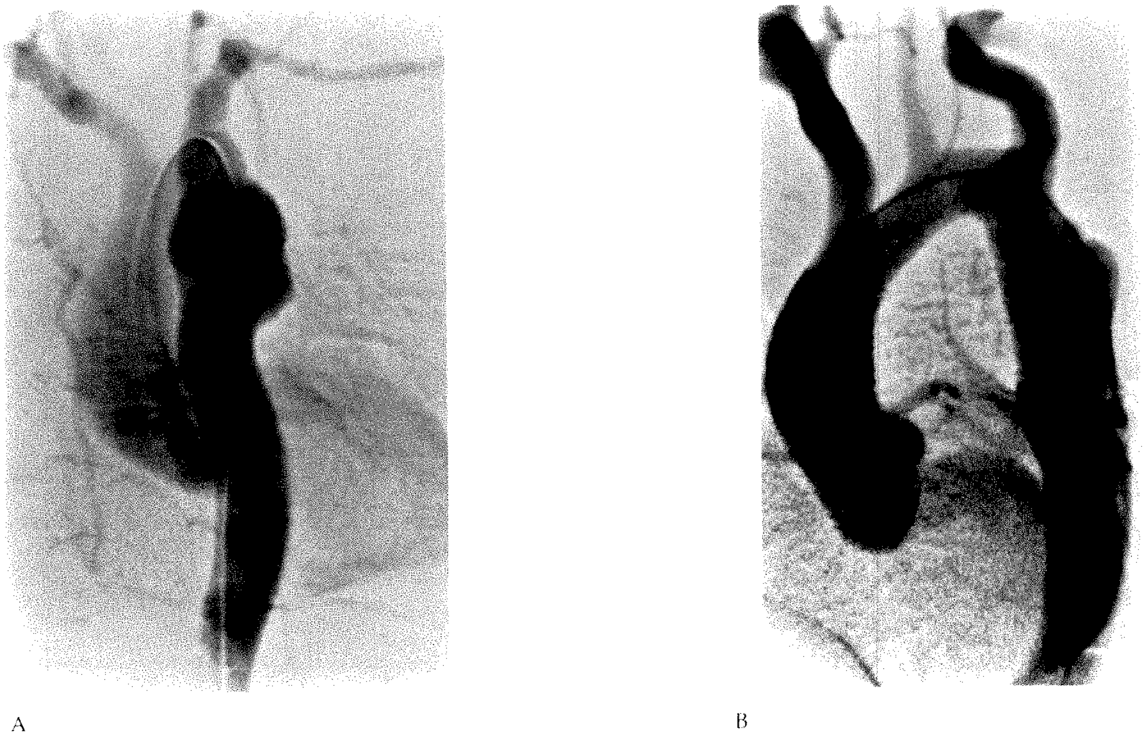

Fig 2. (A, B) Aneurysms at coarctation repair site 18 years after patch aortoplasty. Both aneurysms were suitable for external support.

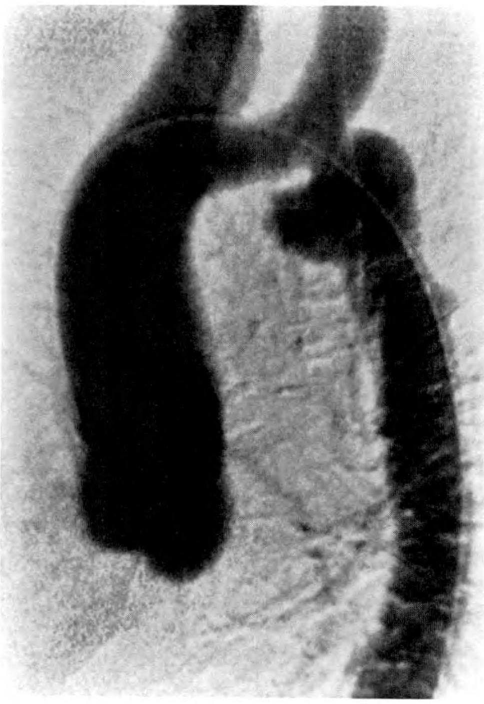

Fig 3. Aneurysm and recoarctation 20 years after patch aortoplasty. Repair with a tubular prosthesis was performed later.

Hg or greater across the area of repair was found twice. To date, these 2 patients have no hypertension or lower limb weakness, and reoperation has been postponed. The neurological deficits noticed after reoperation caused no permanent disability. Paralysis of the phrenic nerve persisted, however. Upper limb claudication (stenosis at the insertion of the left subclavian seen on the angiogram) disappeared gradually without intervention. Other follow-up findings included arterial hypertension (150/90 mm Hg or greater on medication) in 8 (36%) of the 22 patients, aortic valve disease in 6, and ischemic heart disease in 2.

Comment

The exact pathogenesis and incidence of aneurysm formation after patch grafting for aortic coarctation are not known. We [3, 4] and others [5–8] have proposed that the following factors may be involved: congenital or acquired weakness of the aortic wall; the presence of an inelastic graft opposite the aortic wall, which is more compliant; and hypertension and aortic valve insufficiency with an elevated pulse pressure. Of the surgical technical factors, some clinical and experimental evidence indicates that resection of the intimal ridge of the coarctation may weaken the aortic wall and thus cause predisposition to aneurysm formation [7, 9–11]. To our knowledge, our incidence of aneurysm formation is the highest reported; this may reflect the fact that most of our patients were adults when the primary repair was done. Acquired components and prolonged hemodynamic stress may have weakened the aortic wall of these patients. However, the development of an aneurysm in children with a patch graft for coarctation is not unknown [7, 11].

Aneurysm resection with tubular prosthetic replacement is, in most instances, a suitable surgical technique for repair of the aneurysm. We used an external support in 3 patients with a relatively small aneurysm. The main advantage of wrapping is that there is no need for intraoperative heparinization and bypass; bleeding is often a problem after reoperation. However, a small aneurysm cannot be dissected free for wrapping if its bulge projects in the posteromedial direction (see Fig 3).

Paralysis of the recurrent laryngeal nerve was a frequent operative complication. It reflects the difficulty encountered in exposing the aneurysm and adjacent aorta when there is scar tissue. Follow-up revealed that hoarseness after nerve damage was transient; either the nerve regained its function or the vocal cord palsy was compensated for by the opposite cord. A more serious postoperative complication was right-sided hemiparesis, which was experienced by 2 patients. The underlying cause was probably that the proximal aortic clamp, which is placed as necessary between the left carotid and left subclavian arteries, caused stenosis or an embolic event at the former artery during cross-clamping of the aorta. When the wrapping procedure is used, this problem does not arise. Our 2 patients with hemiparesis had no long-term sequelae.

An aneurysm developing after patch graft aortoplasty for coarctation must be treated surgically. Fatal ruptures occur if it is left unattended [3, 7]. Replacement of the aneurysm with a tubular prosthesis gives good long-term results. Our 22 patients underwent reoperation without hospital deaths. However, neurological and bleeding complications were frequent. Close follow-up (radiolog-

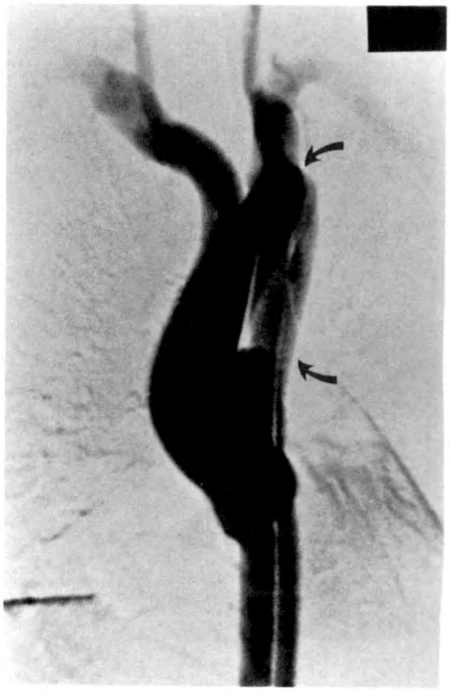

Fig 4. Aortogram made 8 years after reoperation for aneurysm formation after patch aortoplasty. Arrows *mark the position of the tubular prosthesis used for reconstruction of the aorta.*

ical study at least every 1 to 3 years) enables early detection of postoperative aneurysms. In the case of a small aneurysm, the alternative procedure is external support, a procedure that avoids some of the intraoperative difficulties. To date, our experience with long-term results of wrapping is limited, however.

We believe that patch graft aortoplasty should not be used for repair, especially in an adult with aortic coarctation. Our view is contrary to that of some authors [12–14], who recommend the method for primary repair and for reoperation to correct coarctation. Theoretically, leaving the intimal ridge of the coarctation intact in an aortoplasty could decrease (although it could hardly eliminate) the possibility of aneurysm formation; leaving behind an intact intimal ridge, however, might result in incomplete relief of the aortic obstruction in some patients.

Resection and anastomosis or tubular reconstruction in adults and subclavian arterioplasty in children give good results in the primary operation for coarctation. We are analyzing our data on patients who underwent direct isthmusplasty without synthetic grafts. The theoretical disadvantage of that method is that the wall in the region of the coarctation, a wall that may be weak, is left in situ. Indirectly, the follow-up for up to 10 years of our 22 patients indicates that aneurysms do not occur at the coarctation site if the area involved in the coarctation is resected. In addition, we [3] have not found postoperative aneurysms in patients having coarctation repair by methods other than patch graft aortoplasty.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 4, 1990. The closing date for registration is August 1, 1989.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying jfor admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Effect of Surgical Blood Loss and Volume Replacement on Antibiotic Pharmacokinetics

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Antibiotic prophylaxis is used widely to prevent postoperative infection associated with cardiac operations. The influence of perioperative blood loss on antibiotic pharmacokinetics has not been well studied. Plasma cefazolin sodium samples from 8 patients undergoing a cardiac operation were collected postoperatively and analyzed. The results suggest that blood loss has a minimal effect on the elimination of cefazolin and that therapeutic concentrations are maintained without altering the dosage regimen.

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Antibiotic prophylaxis significantly reduces the incidence of infection after a cardiac operation [1]. Cefazolin sodium is often used as a prophylactic agent in these procedures because of its ability to achieve and maintain antibiotic levels exceeding minimum inhibitory concentrations for common pathogens including *Staphylococcus aureus* [2–4]. In addition, it has been shown that cefazolin penetrates well into myocardial tissue and pericardial fluid [5, 6].

Although it has been demonstrated that therapeutic concentrations of antibiotics must be present in the target tissue at the time of incision [7, 8], it is unknown whether therapeutic levels are necessary throughout the immediate postoperative period. Substantial blood loss can take place postoperatively, resulting in large fluid-volume repletion. Massive blood loss and subsequent fluid replacement may result in subtherapeutic antibiotic levels. It is known that low serum antibiotic levels at the conclusion of a cardiac procedure are associated with an increased risk of infection [9]. Furthermore, patients with excessive postoperative bleeding often require emergent reoperation. It is possible that plasma antibiotic levels might be subtherapeutic before reoperation, thus resulting in an increased risk of infection. The effect of blood loss on the kinetics of antibiotics has not been well studied. We elected to determine the effect of perioperative blood loss and volume replacement on cefazolin pharmacokinetics in patients undergoing an elective cardiac operation.

Material and Methods

Patients admitted to the University of California, San Francisco, and scheduled to undergo an elective cardiac procedure were eligible for this study. Patients were excluded from the study if they (1) had a known allergy or hypersensitivity to β-lactam antibiotics, (2) had concomitant or previous antibiotic therapy within 1 week of initiation of cefazolin therapy, or (3) had received concomitant probenecid or any other agent known to alter the active tubular secretion of cefazolin. The study was approved by the committee on human research of the University of California, San Francisco. Written informed consent was obtained from all patients.

A single 1.0-g dose of cefazolin was administered intravenously at the induction of anesthesia. The cardiopulmonary bypass machine also was primed with a 1.0-g dose of cefazolin. Patients were admitted directly to the intensive care unit after completion of the procedure. Five-milliliter blood samples were collected before the first postoperative cefazolin dose (eight hours after the initial dose), at the end of a 30-minute infusion, and 15, 30, 60, 120, 180, 240, 360, and 480 minutes after the end of the infusion. Blood samples were also collected from the chest tube drainage hourly up to 480 minutes after the dose. The exact volume of intravenous fluids, colloids, and blood administered during the postoperative sampling period, as well as the total blood loss, was recorded.

After the samples were drawn, they were immediately placed on ice and centrifuged. The plasma was collected and stored at −20°C until it was assayed. The plasma cefazolin concentration of each sample was determined by a high-pressure liquid chromatography assay developed at the University of California, San Francisco. An Alltech C-8 column was used. The mobile phase consisted of 15% acetonitrile, 15% phosphoric acid, and 0.1% tetramethylammonium chloride titrated to a pH of 7. Spectrophotometric determinations were made at 254 nm with a Waters 441 detector. Cefoxitin was used as the internal standard. The specificity of the assay was 0.5 μg/mL.

Results

Eight male patients scheduled for coronary artery bypass grafting or cardiac valve replacement were enrolled in the study. Age ranged from 62 to 78 years with a mean of 67 years. Patients had estimated creatinine clearances [10] ranging from 39.0 to 80.8 mL/min with an average of 54.7

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Table 1. Effect of Blood Loss on Cefazolin Sodium Elimination

Patient No.	Weight (kg)	Estimated Creatinine Clearance (mL/min)	Half-Life of Cefazolin (h)	Rate of Blood Loss (mL/h)	Trough Concentration (mg/L)
1	96	59.1	2.7	75	7.7
2	72	39.0	9.5	52	59.0
3	68	41.9	16.3	248	153.1
4	81	59.0	2.7	31	17.3
5	48	45.0	4.3	186	22.2
6	106	53.2	2.8	56	20.2
7	96	80.8	2.8	125	12.9
8	79	59.7	3.2	113	8.4
Average	81 ± 18	54.7 ± 13.4	5.5 ± 4.9	111 ± 74	37.6 ± 49.4

± 13.4 mL/min (Table 1). Seven of the 8 patients underwent coronary artery bypass grafting, and 1 had aortic valve replacement. A variety of anesthetics were used including nitrous oxide, isoflurane, and fentanyl.

There was a large degree of variability in the amount of blood loss and fluid replacement (Table 2). The amount of blood lost through the chest tube over the sampling period ranged from 400 to 2,050 mL with a mean of 1,123 ± 562 mL. The rate of blood loss was as high as 248 mL/h. Concomitant fluid replacement reflected the variability in blood loss with an average of 3,180 ± 476 mL (range, 2,694 to 3,945 mL). Calculated cefazolin half-life resulted in a range of 2.7 to 16.3 hours with a mean of 5.5 ± 4.9 hours. The absolute amount of cefazolin lost through the chest tube did not appear to be related to the volume of blood lost. The average amount of antibiotic lost through the chest tube was 139.4 ± 85.3 mg (range, 28.3 to 287.3 mg). Of note, an autotransfuser device was used in 6 patients in this study. However, reinfusion of cefazolin-containing blood did not appear to substantially affect the plasma concentrations.

Cefazolin concentrations immediately before administration of the postoperative dose ranged from 24.0 to 144.7 mg/L with an average concentration of 65.4 ± 38.6 mg/L. The average peak concentration immediately after the dose was 161 ± 91 mg/L (range, 88.8 to 354.4 mg/L). The mean trough concentration eight hours after the dose was measured as 37.6 ± 49.4 mg/L, with the lowest level being 7.7 mg/L (see Table 1).

Comment

All cefazolin concentrations were far in excess of the minimum inhibitory concentration of *S aureus*, a major pathogen in these patients undergoing coronary artery bypass grafting procedures. The minimum inhibitory concentration of cefazolin for *S aureus* in our institution approximates 0.5 mg/L. The lowest observed concentration of cefazolin, independent of blood loss and fluid replacement, was 7.7 mg/L, which is approximately 16 times greater than the minimum inhibitory concentration.

The average half-life of cefazolin in patients with unimpaired renal function is approximately 1.5 hours. The observed half-life of cefazolin in all patients was longer (mean half-life, 5.5 hours) than expected. The observed elevated trough concentrations may be accounted for by

Table 2. Blood Loss and Volume Replacement

Patient No.	Through the Chest Tube: Total Blood Lost (mL)	Through the Chest Tube: Rate of Loss (mL/h)	Cefazolin Lost (mg)	Volume Replacement (mL)
1	900	75	28.3	2,744
2	625	52	100.1	3,700
3	1,490	248[a]	287.3	2,694
4	400	31	. . .	2,790
5	2,050	186	127.3	3,945
6	670	56	. . .	3,279
7	1,500	125	133.4	3,411
8	1,350	113	160.0	2,877
Average	1,123 ± 562	111 ± 74	139.4 ± 85.3	3,180 ± 476

[a] Sampling period was interrupted because the patient had to be returned emergently to the operating room.

the increased half-life. Patient 3, who had the highest rate of blood loss, was noted to have a substantial decrease in his ability to eliminate the drug. His cefazolin half-life was calculated to be approximately 16.3 hours compared with two to three hours in patients who lost blood at lower rates.

More than 95% of cefazolin is eliminated unchanged by the kidneys [11]. Therefore, creatinine clearance is a good estimation of cefazolin elimination. The estimated creatinine clearance was determined through the application of a standard formula developed by Cockcroft and Gault [10]. The estimated creatinine clearance in patient 3 was 42 mL/min; however, this decrease in renal function does not completely account for the marked increase in the cefazolin half-life. Patient 2 had an estimated creatinine clearance that was less than that of patient 3. As expected, his cefazolin half-life was extended, although not to the degree of patient 3 (9.5 hours versus 16.3 hours). If the decrease in elimination of cefazolin was entirely due to the patient's renal status, patient 2 should have demonstrated a longer half-life than patient 3. Patient 2 lost an average of 52 mL/h compared with 248 mL/h for patient 3. It may be that the accelerated blood loss in patient 3 contributed to the pharmacokinetic changes.

The increased cefazolin half-life associated with accelerated blood loss may be explained by certain physiological compensatory mechanisms activated in response to hemorrhagic shock, including decreased renal blow flow. Because cefazolin is primarily eliminated through the kidneys, this acute decrease in blood flow to the kidneys might influence the elimination of the drug. The possibility that the rate of blood loss can alter kidney function and subsequently the elimination of cefazolin appears to be supported by the data derived from the patients in this study.

Our data suggest that cefazolin is widely distributed into the tissues with only a small percentage of the total dose concentrated in the blood. As a result, the total amount of cefazolin in the body is not greatly affected by the loss of blood. This point was demonstrated in this study with the largest amount of cefazolin lost through the blood being 287.3 mg in the patient with the most substantial blood loss. The lowest cefazolin concentration in this patient was 152.1 mg/L. On average, only 14% of the cefazolin dose was eliminated through blood loss in our patients. Therefore, blood loss appears to have a minimal effect on the elimination of cefazolin from patients. It may be that the cefazolin dose added to the heart-lung machine, along with the distribution characteristics and extended half-life of the drug, accounts for this phenomenon.

Autotransfusion of the cefazolin-containing blood did not appear to affect antibiotic concentrations. However, it is important to keep in mind that other drugs, such as heparin sodium, anesthetics, narcotics, and sedatives, will be collected as blood is drained into the autotransfuser device. As a result, when this blood is reinfused into patients, these drugs may result in major pharmacological effects. Drugs that are highly plasma-protein bound or hydrophilic may be important in this regard.

In summary, blood loss after a cardiac operation does not result in a clinically significant loss of cefazolin. Prolongation of plasma half-life was noted in this patient population, which may account for the elevated trough antibiotic concentrations. In addition, although autotransfusion did not result in appreciable increases in plasma cefazolin concentrations, inadvertent administration of other agents, such as heparin, may be taking place. Future studies are necessary to further characterize the pharmacokinetic disposition of antibiotics and other agents in this setting.

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Eighteen to 37 Hours' Preservation of Major Organs Using a New Autoperfusion Multiorgan Preparation

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A new autoperfusion preparation was used to preserve six major organs simultaneously. In 7 Yorkshire white swine, the heart and lungs were separated and removed with the liver, pancreas, duodenum, and both kidneys en bloc while they were self-perfused. Fresh blood, glucose, electrolytes, heparin sodium, methylprednisolone, and a fat emulsion (Soyacal) were infused through the portal vein. No inotropic drugs were necessary. The organs survived for 18 to 37 hours (average survival, 24.6 ± 2.7 hours [± standard error of the mean]). Aortic systolic pressure ranged from 78.5 ± 5.5 to 98.7 ± 11.8 mm Hg. Arterial oxygen tension ranged from 206 ± 23 to 266 ± 15 mm Hg and arterial carbon dioxide tension, from 20.1 ± 2.7 to 32.1 ± 4.9 mm Hg. Blood lactic acid levels decreased from 8.75 ± 2.06 to 5.50 ± 2.45 mmol/L at 24 hours. Urine output ranged from 25 to 82 mL/h. Blood urea nitrogen levels decreased from 9.17 ± 0.59 to 4.67 ± 1.08 mg/dL. Blood creatinine levels decreased from 1.34 ± 0.10 to 0.57 ± 0.22 mg/dL. Serum glutamic-oxaloacetic transaminase levels increased from 73.4 ± 26.3 to 194 ± 179.5 U/L and serum glutamic-pyruvic transaminase levels, from 44.8 ± 5.7 to 91 ± 66.4 U/L. Red blood cell count ranged from 6.94 ± 0.58 to 13.23 ± 2.30 × $10^6/\mu L$. Lung wet/dry weight ratios changed from 5.79 ± 0.17 at the beginning to 6.25 ± 0.16 at 24 hours. The technique for simultaneous multiorgan preservation presented here is simple, effective, and highly reproducible. This study appears to have produced one of the longest average survival times for autoperfusion.

(Ann Thorac Surg 1989;47:860–7)

The increasing clinical application of organ transplantation has stimulated much research into the development of effective organ preservation [1–5]. Improvements in surgical techniques and immunosuppression have led to a growing popularity and interest in combined heart-lung transplantation and even simultaneous multiorgan transplantation [5, 6]. A safe and reproducible technique for long-term organ preservation has not been achieved. Many studies have been directed at extending the survival time of one or two organs to several hours outside the body for potential use in transplantation procedures [7–9]. Short-term simultaneous multiorgan preservation has only recently been achieved in animal experiments [10, 11].

Successful long-term preservation of major organs will not only facilitate combined organ transplantation procedures, but will also improve single-organ transplantation. Because the travel time for donor organs would be extended, a larger pool of organs would be available for transplantation.

This report presents the experimental results of 18 to 37 hours of simultaneous multiorgan preservation using a new autoperfusion technique in which the heart, lungs, liver, pancreas, duodenum, and both kidneys were preserved in combination.

Material and Methods

Animals

Seven Yorkshire white swine ranging in body weight from 30 to 70 kg were used for organ preservation in this study. Another group of 10 Yorkshire white swine of similar body weight was used as the control from which tissue samples were taken from the heart, lung, liver, kidney, pancreas, and duodenum for normal tissue wet/dry weight ratios.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Surgical Technique

Before the operation, neomycin sulfate (2 g/day) was given for three days to sterilize the gastrointestinal tract. The procedure used to harvest the organs was similar to the one published previously for dogs [10]. Some modifications were made. A brief description follows.

The animal was anesthetized with sodium pentobarbital (30 mg/kg), intubated, and artificially ventilated.

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Before the operation, venous blood samples were taken from the jugular vein for complete blood count and measurements of blood chemistries (K^+, Na, Cl^-, Ca^{2+}), enzymes (serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, creatine kinase, lactate dehydrogenase, isoenzymes of lactate dehydrogenase, amylase), blood urea nitrogen, and creatinine. Arterial blood samples were also taken for measurement of pH, arterial oxygen tension, and arterial carbon dioxide tension. These variables were used as normal controls for later comparison with those obtained during the preservation period.

With the animal in the supine position, the abdomen was opened and the liver, pancreas, duodenum, and both kidneys, as well as the abdominal aorta and inferior vena cava, were dissected free. The spleen was removed, and one catheter was placed in the splenic artery for measurement of systemic blood pressure. Another catheter was placed in the portal vein through the splenic vein for infusion of blood and fluids. The abdominal aorta and inferior vena cava were divided below the renal branches, and a catheter was placed in the inferior vena cava for central venous pressure monitoring and blood sampling.

The diaphragm was incised around the liver. The chest was then opened and the heart and lungs, along with the aorta and superior and inferior vena cavae, were dissected free. LDS Powered Staplers (US Surgical, Norwalk, CT) were used to divide the intercostal arteries. The trachea was divided and intubated for ventilation using a Harvard respirator. A left ventricular catheter (8F) was placed through the right carotid artery for pressure measurement. The common bile duct and the duodenum were cannulated for fluid collections. Two catheters were placed in the ureters for urine collection.

The whole system (Fig 1) was then removed en bloc and placed in a water bath containing lactated Ringer's solution, heparin sodium (10 mg/L), neomycin sulfate (0.5 g/L), and penicillin (100,000 U/L).

Interventions

The temperature was maintained at 32°C by heating the water bath with a constant-temperature circulator. Artificial respiration was maintained with a Harvard volume-cycled respirator at a tidal volume of 300 to 500 mL, a rate of 10 to 20 rpm, and a positive end-expiratory pressure of 2 to 6 cm H_2O. A gas mixture of 50% O_2 + 3% CO_2 + 47% N_2 was utilized. The following solution was given through the portal vein at a rate of 10 to 20 mL/h: dextrose 10% containing potassium chloride, 2 g/L; calcium chloride, 1 g/L; insulin, 100 U/L; mannitol, 12.5 g/L; methylprednisolone, 250 mg/L; heparin, 50 mg/L; penicillin, 1,000,000 U/L, and Flagyl (metronidazole hydrochloride), 500 mg/L. A fat emulsion (Soyacal) (2 mL), methylprednisolone (30 mg), and heparin (20 mg) were delivered through the portal vein every two hours. Blood transfusions were given to maintain aortic systolic pressure between 75 and 100 mm Hg and central venous pressure between 0 and 10 mm Hg. Plasma was replaced instead of whole blood if the hematocrit was higher than 45%.

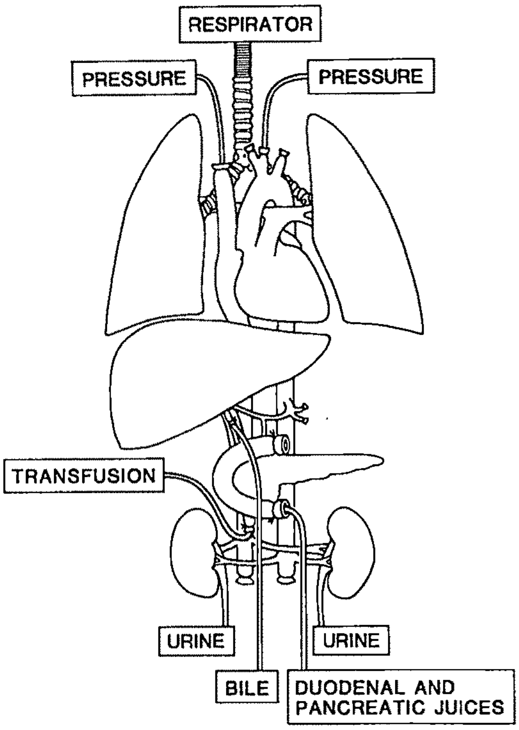


Fig 1. Simultaneous multiorgan autoperfusion preservation in which the heart, lungs, liver, pancreas, duodenum, and both kidneys are preserved in one system. No foreign material is used to assist the circulation. Reproduced from [10] with permission from The C.V. Mosby Company.

Monitoring

Aortic pressure, left ventricular pressure, central venous pressure, and portal venous pressure were monitored and recorded on a SensorMedics R612 Dynograph recorder (Anaheim, CA) throughout the preservation period. Temperature, urine output, bile production, and duodenal and pancreatic secretions were collected and recorded every hour. Visual changes including color, size, and bleeding of each organ and respiratory pressure, tidal volume, and positive end-expiratory pressure for the

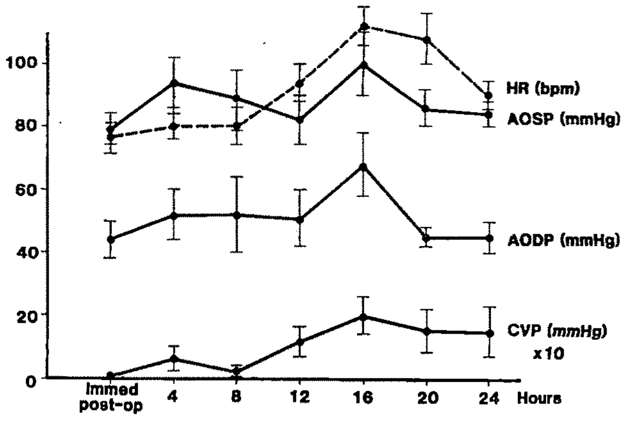


Fig 2. Change in heart function during 24-hour period. (AODP = *aortic diastolic pressure;* AOSP = *aortic systolic pressure;* CVP = *central venous pressure;* HR = *heart rate.)*

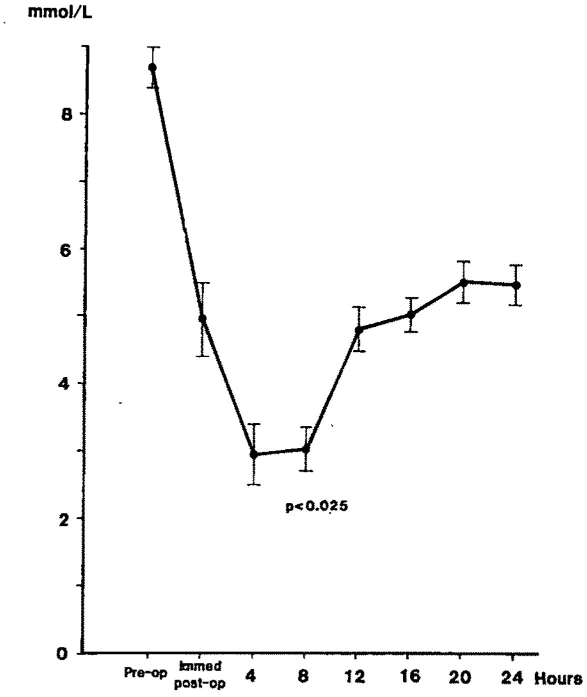


Fig 3. Blood lactic acid levels during preservation period.

lungs were recorded every hour. Arterial blood gas and hematocrit measurements were performed every hour. Venous blood samples were taken every four hours during the preservation period and used for blood chemistries, hematology, and enzyme measurements for heart, liver, pancreas, and kidney functions. Tissue samples were taken from the lungs immediately after the operation and every four hours for determination of the tissue wet/dry weight ratio and electron microscopic studies. At the termination of the study, specimens were taken from each organ for measurement of tissue wet/dry weight ratios and pathological examinations.

Determination of Tissue Wet/Dry Weight Ratio

Tissue samples used for wet/dry weight ratio measurements were blotted to remove excess fluid, and wet weight was measured. The dry weight was determined

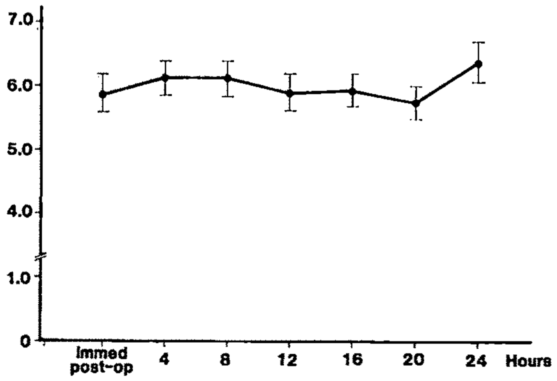


Fig 5. Change in lung tissue wet/dry weight ratios.

after the samples had been in an oven at 85°C for 72 hours.

Statistical Analysis

Variables measured immediately postoperatively and during the preservation period were compared with normal values obtained preoperatively using paired and unpaired Student's *t* tests. Organ tissue wet/dry weight ratios after preservation were compared with the samples obtained from normal pigs. The level of significance was 0.05.

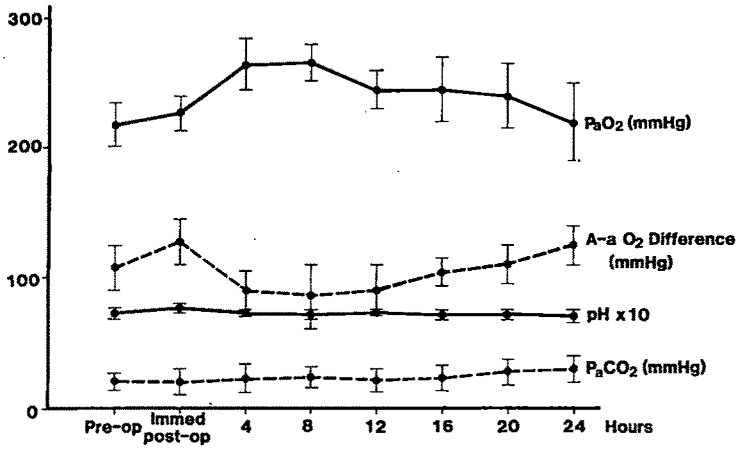
Results

The mean survival time of the organs was 24.6 ± 2.7 hours (± standard error of the mean) (range, 18 to 37 hours). Cardiac arrest resulting from clots in the coronary artery caused "sudden death" in 2 of the systems. Severe infection resulted in the deaths of an additional 2 systems.

Cardiac Function

Aortic systolic pressures ranged from 78.5 ± 5.5 to 98.7 ± 11.8 mm Hg during the preservation period, and were easily adjusted by blood or plasma infusion (Fig 2). No inotropic drugs were necessary. Aortic pulse pressure ranged from 29.1 ± 2.6 to 41.0 ± 2.7 mm Hg, and did not fluctuate appreciably during the preservation period. (Immediately after the operation it was 35 ± 2.7 mm Hg and

Fig 4. Change in blood gas values over 24 hours of preservation. (A-a O_2 Difference = *alveolar-arterial oxygen tension difference;* $PaCO_2$ = *arterial carbon dioxide tension;* PaO_2 = *arterial oxygen tension.)*



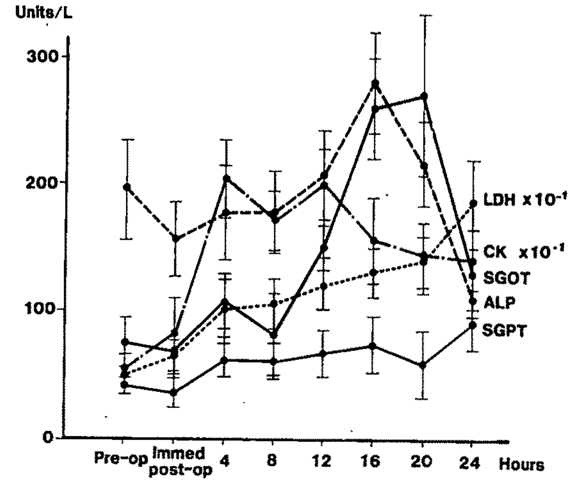


Fig 6. Changes in blood enzymes during 24-hour period. At 24 hours, the creatine kinase (CK) *value was significantly different from the preoperative value* ($p < 0.05$). (ALP = *alkaline phosphatase;* LDH = *lactate dehydrogenase;* SGOT = *serum glutamic-oxaloacetic transaminase;* SGPT = *serum glutamic-pyruvic transaminase.)*

at 24 hours, 40.0 ± 3.3 mm Hg.) Central venous pressure ranged from 0 to 2.1 ± 1.8 mm Hg. Heart rate ranged from 67 ± 5 to 122 ± 15 beats per minute, and there were two occurrences of arrhythmia. Blood lactic acid levels decreased from a preoperative value of 8.75 ± 2.06 mmol/L to 3.03 ± 0.98 mmol/L at eight hours ($p < 0.025$) and 5.50 ± 2.45 mmol/L at 24 hours (Fig 3). Serum creatine kinase level increased gradually during the preservation period ($p < 0.05$ at 24 hours).

Lung Function

Arterial oxygen tension ranged from 206 ± 23 to 266 ± 15 mm Hg and arterial carbon dioxide tension, from 20.1 ± 2.7 to 32.1 ± 4.9 mm Hg. Alveolar-arterial oxygen tension differences ranged from 86 ± 12 to 125 ± 18 mm Hg, and the arterial pH value ranged from 7.33 ± 0.03 to 7.52 ± 0.03 (Fig 4). In 3 systems, the lungs sustained varying degrees of pressure damage. Lung wet/dry weight ratio was 5.79 ± 0.17 at the beginning of the experiment (Fig 5). It changed to 5.82 ± 0.30 at 12 hours and did not increase at 20 hours. This ratio had increased to 6.25 ± 0.16 at 24 hours, but the increase was not significant ($p > 0.1$).

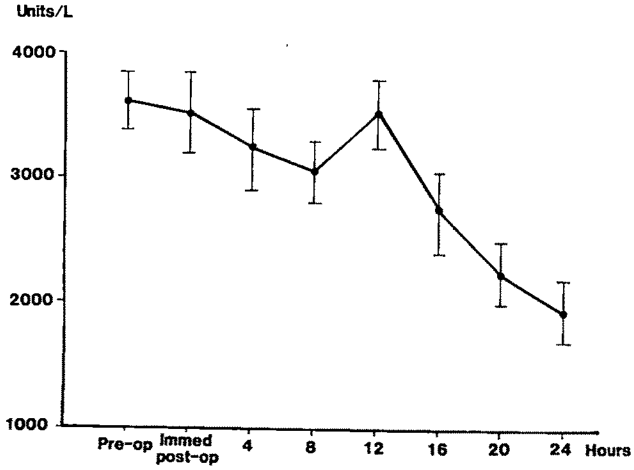


Fig 7. Changes in blood amylase levels during 24-hour period.

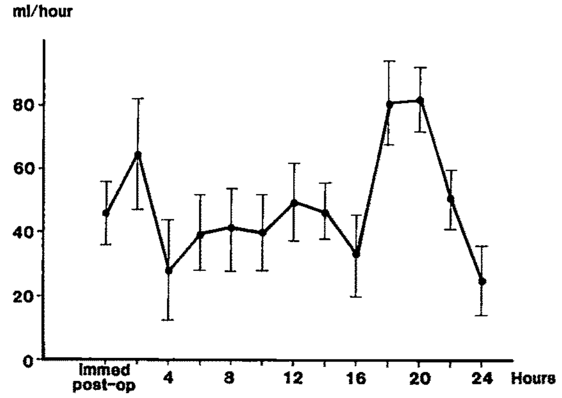


Fig 8. Urine output during 24-hour period.

Liver Function

Total bile output during the preservation period ranged from 15 to 80 mL with a range of 0.8 to 2.2 mL/h. The liver demonstrated good preservation and appeared normal throughout the preservation period in 4 systems. In 3 of the systems, some patchy darkening and localized edema appeared in the liver after 12 hours of preservation. Laboratory tests for liver-related enzymes showed moderate increases in serum glutamic-oxaloacetic transaminase, alkaline phosphatase, and lactate dehydrogenase levels and only a slight increase in the serum glutamic-pyruvic transaminase level (Fig 6).

Pancreatic and Duodenal Function

In 4 of the systems, the pancreas and duodenum showed normal color and size. In 3 preparations, clots formed around the catheter in the splenic vein and extended to

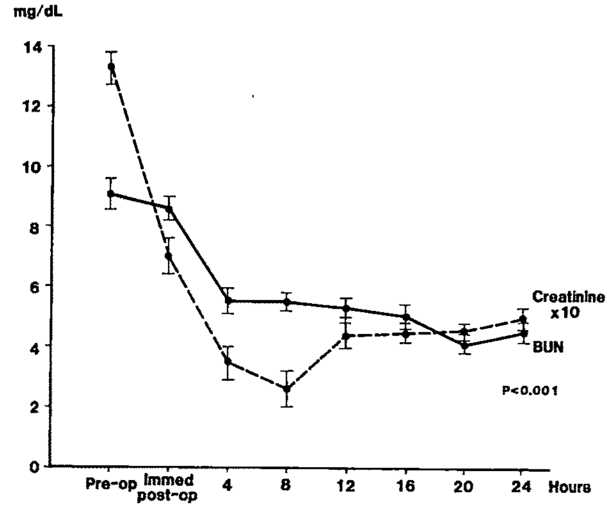


Fig 9. Changes in blood urea nitrogen (BUN) *and creatinine levels during 24-hour period.* ($p < 0.001$ *at 24 hours for both BUN and creatinine.)*

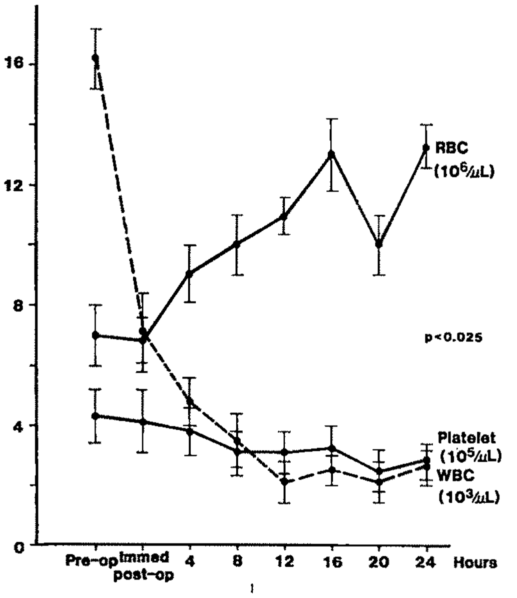


Fig 10. *Changes in blood cells during preservation.* (RBC = *red blood cell;* WBC = *white blood cell.)*

the portal vein, causing venous return blockage; the pancreas and duodenum showed congestion. Secretions from these two organs ranged from 1 to 18 mL/h (total, 25 to 450 mL). Blood amylase levels decreased during the preservation period (Fig 7).

Renal Function

Total urine output ranged from 800 to 1,500 mL with hourly urine output ranging from 25 to 82 mL (Fig 8). All kidneys showed normal size, color, and function during the preservation period. Blood urea nitrogen levels decreased from 9.17 ± 0.59 mg/dL before the operation to 4.67 ± 1.08 mg/dL at the end of 24 hours ($p < 0.001$). Blood creatinine levels decreased by 80% at eight hours ($p < 0.0001$) and maintained a significantly low level throughout the experiments ($p < 0.001$ at 24 hours) (Fig 9).

Hematological Study

Red blood cell concentrations increased from 6.94 ± 0.58 × $10^6/\mu L$ to 13.23 ± 2.30 × $10^6/\mu L$ during preservation as a result of exudation of lymph fluid ($p < 0.025$ at 24 hours) (Fig 10). Plasma transfusions were required in all of the experiments to maintain a low hematocrit. White blood cell counts showed a continuous decrease during the preservation period ($p < 0.025$ at 24 hours). Blood platelet levels also showed some decrease during the preservation period ($p < 0.025$ at 24 hours). Free plasma hemoglobin had a twofold increase at 24 hours (from 13.8 ± 5.1 to 29.9 ± 12.9 mg/dL; $p > 0.1$) (Fig 11).

Blood Chemistry

Potassium, calcium, and glucose were replaced as needed to maintain normal levels in the blood. Blood sodium, chloride, and phosphorus levels increased slightly but remained in the normal range during the preservation period (Fig 12).

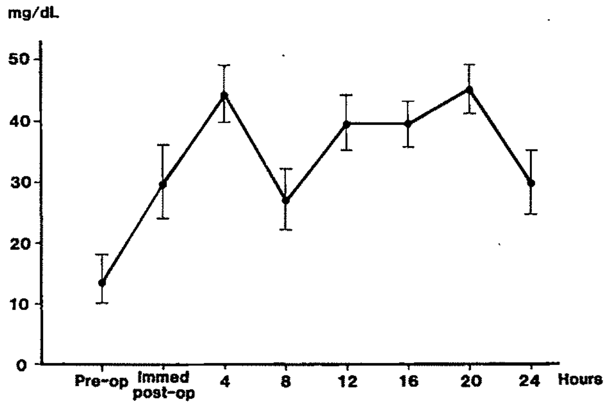


Fig 11. *Change in free plasma hemoglobin.*

Tissue Wet/Dry Weight Ratios After Preservation

Tissue samples from all the organs were compared with samples obtained from normal pigs. There was almost no increase in wet/dry weight ratio for the heart. There were some increases in this ratio for the lung, liver, kidney, pancreas, and duodenum, but only the increases for the kidney and liver appeared to be significant (Fig 13).

Pathological Study

Electron microscopic studies of lung tissue samples showed good tissue preservation for up to 20 hours. There was moderate interstitial widening caused by edema at 20 to 24 hours in some systems. Samples from the heart, liver, pancreas, duodenum, and kidney were essentially normal at 20 to 24 hours in the long survival preparations.

Comment

Preservation of human organs for transplantation has been a challenge to all transplant surgeons and a subject of many studies [12–14]. The kidney can be preserved by hypothermia for more than 24 hours, but other organs, such as the heart, lung, liver, and pancreas, can be kept viable for only a few hours before transplantation [8]. Development of techniques that would allow extension of an organ preservation period to 24 hours or more, especially for organs such as the heart, lung, and liver, would dramatically increase both the number of potential donor and recipient matches and the likelihood of their success [15].

Starling created the first autoperfusion heart-lung preparation for studies in physiology in 1920 [16]. Demikhov used this technique for transplantation in 1948 [17], and Robicsek and co-workers [18] applied this technique for heart-lung preservation studies in 1959. However, uniform and consistent results that demonstrated successful preservation of organs for more than 20 hours were not obtained, and research on autoperfusion as a tool for preservation almost ceased by 1976, as evidenced by the exclusion of this procedure in reviews of organ preservation techniques [19]. Because there is no period of ischemia during the harvesting and preservation periods of this procedure, interest in autoperfusion has recently

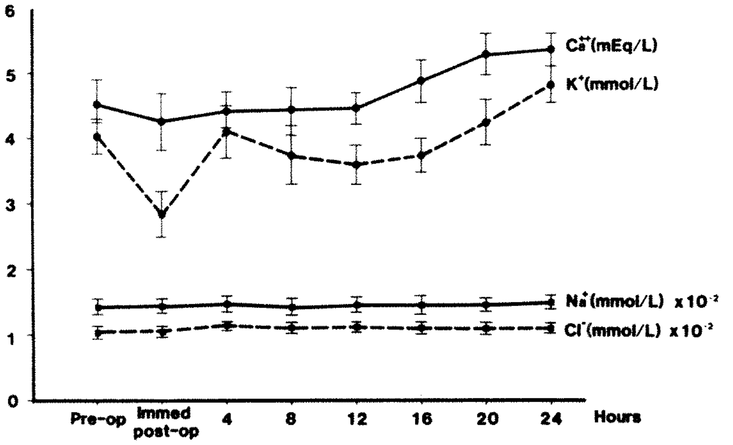


Fig 12. Changes in blood potassium (K^+), *sodium* (Na^+), *chloride* (Cl^-), *and calcium* (Ca^{++}) *during preservation.*

been renewed. An example of this was the studies by Hardesty and Griffith [20], who reported the clinical results of using autoperfusion for distant heart and lung procurement in 1987.

Autoperfusion also has the advantages of normal blood circulation and natural tissue and vascular connections. Expansion of the autoperfusion technique to preserve a group of organs was recently tried in dogs. The heart, lungs, liver, pancreas, duodenum, and both kidneys were preserved together for an average of 12 hours as reported by our group [10], and the heart, lungs, liver, pancreas, spleen, small intestine, and both kidneys were preserved for an average of six hours as reported by Prieto and colleagues [11] at the University of Minnesota. Although these preservation times are not long enough to have practical clinical implications, the expansion of the autoperfusion technique to a multiorgan preparation may provide insight into the concept that harvesting all the major organs without disturbing the blood supply (and thus eliminating organ ischemic time) may indeed be of major practical importance in transplantation procedures. The combined preservation of major organs may also reduce or eliminate the potential for tissue destruction of an individual organ during the period of harvesting [21].

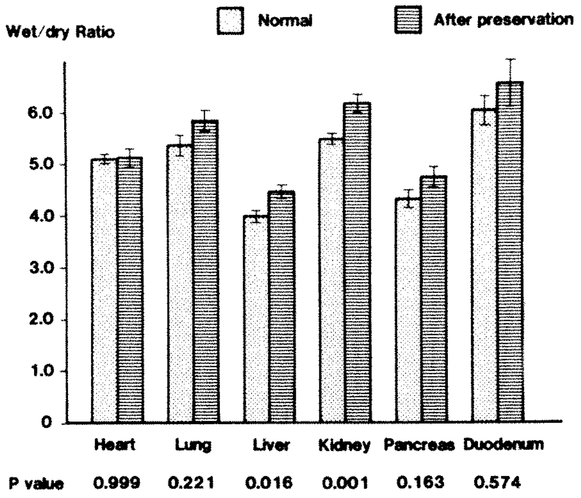


Fig 13. Comparison of tissue wet/dry weight ratios in experimental group and normal group.

In the study involving dogs, the liver is responsible for restricting the survival time of the multiorgan system. The canine portal circulation is extremely prone to infection, and ischemia of the liver results in contraction of the hepatic vein sphincters, producing an obstruction to venous outflow [22]. Even though the other organs are physiologically functional, liver congestion causes a reduced effective circulation volume, impaired liver function, and finally, deterioration of the whole system. The resulting premature "death" is due not to the failure of the whole system, but to the failure of one organ. This phenomenon does not occur in the pig or humans [22], which was the main reason we decided to study pigs.

The heart was one of the most well preserved organs in this study. Normal heart function was maintained throughout the preservation period as shown by pressures, heart rate, lack of arrhythmias, and freedom from inotropic support. There was minimal change in the color and size of the heart, and myocardial wet/dry weight ratios were almost normal at the end of experiment. The pericardium did not have to be manipulated in any of the systems because of an enlarged heart or fluid accumulation in the pericardium. The average heart rate in the preparation was lower than that for normal intact pigs. This was most probably related to the lower temperature used during the preservation experiments.

The organ system appeared to be able to maintain the pressure without nervous regulation, as no inotropic drugs were necessary at any time and the adrenal gland was not included in the harvesting. It was also shown in previous studies using only the heart, lungs, and kidney that no inotropic support was necessary [23].

Compared with the heart, the lungs of the pig were not ideal for preservation. In our study, we found that although lung function remained satisfactory during the preservation period and lung tissue wet/dry weight ratio showed only minimal changes at 24 hours, the lungs were easily damaged by minor increases in pressure. When we were trying to expand a small area of collapsed lung, a whole lobe of already expanded lung would frequently burst, resulting in continuous bleeding and air leakage.

Histologically, there was less connective tissue among the alveoli of porcine lungs when compared with canine or human lungs. It is not clear whether this is characteristic of all porcine lungs or only those of the particular species of pigs used. In later experiments, we routinely used a release valve on the inspiration tubing so that the inspiratory pressure would not exceed 10 cm H_2O. This resulted in better lung protection. Accordingly, however, the sensitivity of the lungs to pressure is a major disadvantage when pigs are used for lung preservation studies. If some other farm animals with tougher lungs were used, the preservation time could be extended.

Because of its bulky size, irregular surface, and fast metabolism, preservation of the liver is more difficult than preservation of some other organs. In this study, the liver was relatively well preserved. Laboratory tests showed some increase in the levels of liver-related enzymes including serum glutamic-oxaloacetic transaminase, lactate dehydrogenase, and alkaline phosphatase, with serum glutamic-oxaloacetic transaminase and lactate dehydrogenase more prominent. However, these three enzymes have widespread tissue distribution, and interpretation of these enzymes as related to a specific organ is difficult if no other measurements are made. Incision of skeletal muscle during the operation, hemolysis during preservation, use of high doses of heparin and methylprednisolone, and infection in the system might all contribute to the increase of these enzymes [24]. The increase of alkaline phosphatase was probably related to infection in the system. Also, the increase of enzymes was not uniform. In 2 preparations, the increase was minimal, and in another 2, there were no enzymatic increases. In preparations in which enzymatic values were high, premature death occurred, which lowered the pooled average values. The more specific liver enzyme, serum glutamic-pyruvic transaminase, increased only minimally during the preservation period. Microscopic examination of the liver revealed only minor histological changes. Because the liver does not have any ischemic time using this technique, the potential for use in liver preservation studies should be evaluated.

Special attention should be paid to the correct alignment of the liver when this technique is used. The liver is specially subject to torsion when removed from the body because of its large size and the slim vascular connections between the liver and the heart. The liver tended to sink while the lungs were floating when placed in the water bath [10]. We used a stand to support the abdominal organs so that all the organs were kept in the same plane. However, a large change in the level of the bath solution would often cause torsion of the inferior vena cava. Such torsion and increased blood flow resistance might have contributed to some accumulation of water in the abdominal organs.

This is one of the very few reports in which the duodenum and pancreas were preserved with a "no-ischemic" technique. Preservation of a longer part of intestine or even the whole intestine may be desirable if intestinal transplantation is the primary concern. In our pilot studies, however, we found that denervation of the intestine led to abnormal functioning. In addition, the larger the amount of intestine preserved, the higher the risk of infection.

The kidneys functioned well throughout the preservation period. Laboratory tests for blood urea nitrogen and creatinine indicated good renal function. This could be very important in long-term organ preservation, as the removal of excessive water and metabolic wastes is vital for tissue protection. In this study, there was no unusual tissue edema or pericardial effusion during the preservation period. This was clearly related to the kidney's removal of extra water in the circulation. Our previous experiments have also shown the importance of the kidney in autoperfusion [23].

Red blood cell damage, as demonstrated by the small increase in free plasma hemoglobin level at 24 hours, was minimal in relation to the damage found with other autoperfusion techniques [25]. This was probably due to the fact that the blood was circulating naturally, with no foreign materials involved. In 5 of the preparations, free plasma hemoglobin increased suddenly during blood transfusions and decreased gradually after one to two hours. We believe this was caused mainly by untyped blood used for transfusion.

There was a considerable reduction in white blood cells during the preservation period. The decrease was probably related to either infection in the system or sequestration of white blood cells in the lungs. Because the preparation contains no bone marrow, any infection would cause a reduction in white blood cells. In microscopic studies, white blood cell deposits were found in the lung tissue sections. This could be related to lung tissue damage [26, 27] and is under further investigation in our laboratory.

Exudation of lymph was prominent in the early postoperative period. The chest duct was cannulated in some experiments, and the lymph drainage ranged from 20 to 100 mL/h during the first three to four hours. It decreased gradually after three to four hours of the preservation period. We modified our surgical procedure in some preparations to include venous dissection of the left subclavian, which protects the chest duct, and lymph loss was substantially reduced.

An important consideration in this study was the high coagulation state of the pig. In our study, even when the operation was done rapidly and large masses of tissue were surgically excised without ligation, postoperative bleeding was not a major concern. On the other hand, strict attention was given to prevent clotting. Heparin was routinely infused immediately after the system was taken from the body, and 20 mg of heparin was injected every two hours. Clots in the main coronary arteries were still found in 2 preparations and caused premature death of the whole system. Clot formation usually occurred after a long period of high hematocrit (60% or more). Although the dose of heparin used was high, the amount employed may not have had a sufficient anticoagulant effect for those preparations with high hematocrit and mild hypothermia. The deaths should be preventable by close monitoring of the level of heparin and maintaining a low or normal hematocrit.

Our study had some limitations. These include fragile lungs and high blood coagulability in pigs. Also, because of limitations of the laboratory environment, most of our experiments were performed under semisterile conditions. Bacterial infection usually occurred after 12 hours of preservation, which resulted in deterioration and death in 2 of the organ systems. This kind of death would be avoidable in a properly controlled environment.

The system is relatively large compared with a single organ. However, the setup is very simple, as only a respirator is necessary to maintain normal function. The whole system is portable, allowing for transportation over long distances. Our final goal is to keep the organs viable as a group for several days or longer so there will be time for delivery anywhere in the world. This amount of time would allow retrieval, transport, and implantation of organs in a more systematic and controlled manner. Such long-term preservation also has possibilities for the establishment of transplantable organ banks.

Despite the problems, the overall results of this study seem very promising. The advantages of this technique are the absence of a period of ischemia, which allows major organs to be preserved without damage, and a natural circulation without foreign material, which makes long-term multiorgan preservation possible. The unique natural connections between all the preserved organs will also facilitate simultaneous multiorgan harvesting and transplantation. To our knowledge, this study has yielded the longest average survival times for organs with the technique of autoperfusion.

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Tension Pneumothorax During Extracorporeal Membrane Oxygenation

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Life-threatening tension pneumothorax in neonates on extracorporeal membrane oxygenation (ECMO) has been associated with an increase in arterial oxygen tension and a decrease in peripheral perfusion, followed by a decrease in ECMO flow with progressive hemodynamic deterioration. To investigate this triad, chest tubes were placed bilaterally in 9 dogs to allow injection of air to produce tension pneumothorax. Six dogs were subsequently placed on standard venoarterial ECMO before the reinduction of tension pneumothorax. Measured values included arterial pulse pressure, inferior vena cava pressure, systemic arterial blood gases, peripheral arterial oxygen saturation, mixed venous oxygen saturation, and left heart cardiac output. Oxygen delivery was calculated from directly measured values. Each of the 6 dogs on ECMO demonstrated the triad of increased arterial oxygen tension (92 ± 7 to 325 ± 20 mm Hg; $p < 0.05$), decreased peripheral perfusion (as evidenced by a decrease in pulse pressure from 55 ± 4 to 31 ± 5 mm Hg; $p < 0.05$), and decreased mixed venous oxygen saturation (71% ± 3% to 22% ± 2% saturation; $p < 0.05$) followed by a lower ECMO flow with progressive hemodynamic deterioration (oxygen delivery decreased from 285 ± 11 to 111 ± 12 mL/min; $p < 0.05$). Aspiration of the intrathoracic air allowed return to baseline ECMO flow and hemodynamic stability in all dogs. The triad of increased arterial oxygen tension and decreased peripheral perfusion (as evidenced by a lower arterial pulse pressure and lower mixed venous oxygen saturation) followed by decreased ECMO flow with progressive hemodynamic deterioration consistently appears when tension pneumothorax occurs on ECMO.

(Ann Thorac Surg 1989;47:868–71)

Extracorporeal membrane oxygenation (ECMO) has been successful (greater than 80% survival) in 42 centers for more than 1,800 newborns with severe respiratory failure, who have an estimated mortality of greater than 80% with conventional management [1]. Extracorporeal membrane oxygenation is prolonged extracorporeal cardiopulmonary bypass achieved by extrathoracic vascular cannulation of the internal jugular vein (for removal of blood from the right atrium) and the common carotid artery (for return of oxygenated blood to the aortic arch). Tension pneumothorax has been reported in ECMO patients demonstrating a triad of increased peripheral arterial oxygen tension (PaO_2), decreased peripheral perfusion, and decreased ECMO flow with progressive hemodynamic deterioration [2]. We developed a canine model of progressive tension pneumothorax on ECMO to investigate the pathophysiology and verify the proposed triad associated with life-threatening tension pneumothorax on ECMO.

Material and Methods

Nine adult mongrel dogs weighing 14 to 16 kg were anesthetized with intravenous administration of sodium pentobarbital (25 mg/kg), which was maintained throughout the experiment by bolus (5 mg/kg) injection as required. The animals were intubated, placed in the supine position, and mechanically ventilated with room air. Core temperature was maintained by a heating pad. A thermistor-tipped catheter was placed into the abdominal aorta through the right femoral artery for measurement of arterial pulse pressure, mean arterial pressure, and left ventricular cardiac output (CO) by thermodilution. A 12-gauge central venous line was inserted through the right femoral vein for the measurement of venous blood gases and inferior venal caval pressure and for the administration of medications. A 12-gauge catheter placed in the left ventricle through the left common carotid artery was used for the injection of iced saline solution (4°C) for left ventricular CO determination. Baseline data were collected after the catheters were inserted.

Chest tubes (16F) were placed bilaterally into the pleural cavity through the fourth interspace. Each tube was equipped with a stopcock and a 60-mL syringe for injection and aspiration of air. Intrapleural air introduced during chest tube placement was removed, and the animal was allowed to recover. Each dog served as its own control.

Initially, we established the canine model of tension pneumothorax (control). Air was injected into the intrapleural space in 300-mL increments to a maximum of 200 mL/kg. Data were collected five minutes after each 300 mL of air was introduced. The acid-base status was corrected as necessary with intravenous administration of sodium bicarbonate. After data collection at maximum tension pneumothorax (200 mL/kg), all air was aspirated from the

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intrapleural space, and the volume of air removed was verified with the volume infused. The animal was allowed 30 minutes for recovery.

In 6 dogs (ECMO group), standard venoarterial ECMO [3–5] was then instituted for partial cardiopulmonary support (60 mL/kg/min). A 14F Elecath cannula (Elecath Corp, Rahway, NJ) was placed into the right atrium through the right internal jugular vein, and a 10F Argyle cannula (Sherwood Medical, St. Louis, MO) was placed into the aortic arch through the right common carotid artery. Venoarterial bypass was accomplished by drainage of blood from the right atrium into a modified heart-lung machine, which consists of a venous reservoir, a servo-regulated roller pump that stops when venous drainage is inadequate, a SciMed Kolobow spiral-coil membrane lung (SciMed Life Systems, Inc, Minneapolis, MN) to exchange oxygen and carbon dioxide, and a SciMed heat exchanger to maintain normothermia. Continuous heparin anticoagulation was titrated to maintain the whole-blood activated clotting time according to the Bason method [6] greater than 240 seconds by ACTester (TriMed, Huntington Beach, CA) to prevent thrombosis of the circuit. Before ECMO, a loading dose of bovine lung heparin (300 mL/kg) was administered, and the activated clotting time was verified to be greater than 240 seconds. Mixed venous oxygen saturation (SvO_2) was monitored continuously by an Oximetrix (Abbott Laboratories, North Chicago, IL) catheter inserted into the venous tubing of the ECMO circuit. The animal was maintained on ECMO for 30 minutes before the baseline data were collected.

During ECMO, the same protocol for tension pneumothorax was followed; air was injected into the intrapleural space in 300-mL increments to a maximum of 200 mL/kg. Data were collected five minutes after each 300 mL of air was injected. Acid-base status was corrected using intravenous administration of sodium bicarbonate as necessary during periods of low perfusion. When venous return became reduced beyond that necessary to sustain ECMO flow at 60 mL/kg/min, the servo-regulated ECMO pump stopped to prevent air embolism. Injection of air continued to maximum tension pneumothorax. After data collection at maximum tension pneumothorax (200 mL/kg), all air was aspirated and the volume of air removed was verified with the volume infused. Data were collected every ten minutes for an additional 30 minutes to monitor recovery before termination of the experiment.

Hemoglobin was measured at the beginning of data collection and after the animal was on ECMO for 30 minutes. Oxygen content and oxygen delivery (Do_2) were calculated based on systemic arterial samples analyzed for blood gases (pH, carbon dioxide tension, oxygen tension [Po_2], oxygen saturation (O_2 sat), hemoglobin (Hb), and CO. Systemic arterial oxygen content and systemic Do_2 were calculated from these directly measured values using the following formulas [7]:

$$\text{Oxygen content} = (O_2\ \text{sat})(\text{Hb})(1.36) + (Po_2)(0.003)$$

$$Do_2 = (\text{CO/kg})(\text{oxygen content}).$$

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Data are reported as the mean ± the standard error of the mean. Analysis was performed using Student's *t* test to compare ECMO tension pneumothorax with ECMO baseline and to compare ECMO tension pneumothorax with control tension pneumothorax.

Results

Our initial effort was to establish a canine model of tension pneumothorax that could be used for both control and ECMO groups. The results are summarized in Figure 1. In the control dogs (tension pneumothorax group), tension pneumothorax demonstrated a pathophysiology of increased intrathoracic volume (as evidenced by an increased inferior vena caval pressure) and a decrease in venous return, which led to the classic hemodynamic sequelae of tension pneumothorax [8]. These trends can be summarized as follows: decreased pulse pressure,

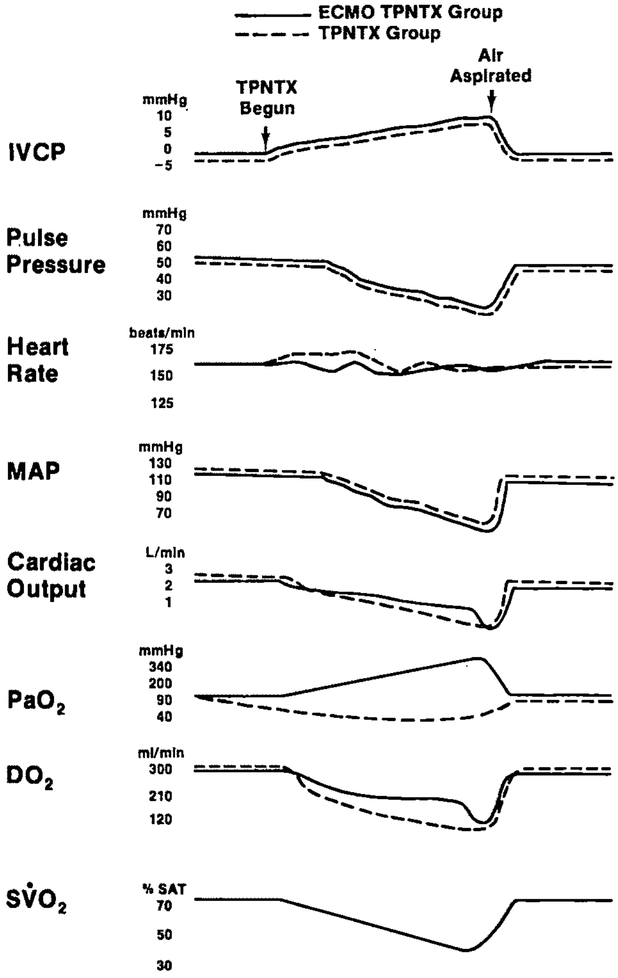

Fig 1. Changes during the development of tension pneumothorax (TPNTX) *in both the extracorporeal membrane oxygenation* (ECMO) *pneumothorax group and the control pneumothorax group.* (DO_2 = *oxygen delivery;* IVCP = *inferior vena cava pressure;* MAP = *mean arterial pressure;* PaO_2 = *arterial oxygen tension;* SVO_2 = *mixed venous oxygen saturation.*)

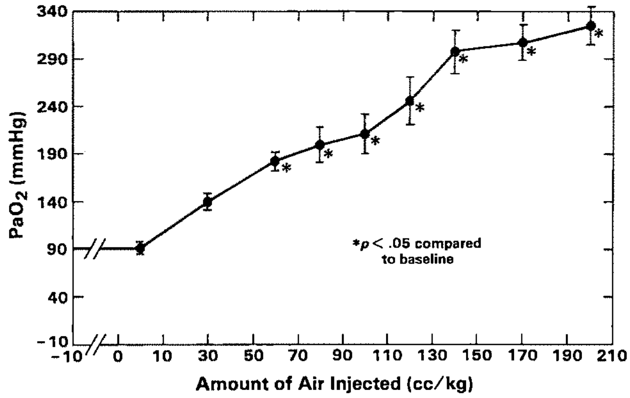

Fig 2. Rise in arterial oxygen tension (PaO_2) as tension pneumothorax develops while on extracorporeal membrane oxygenation.

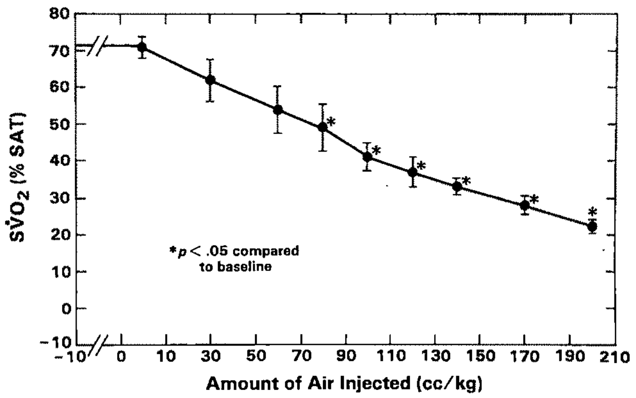

Fig 4. Decline in mixed venous oxygen saturation (SVO_2) as tension pneumothorax develops while on extracorporeal membrane oxygenation.

decreased mean arterial pressure, decreased CO, and decreased PaO_2. Subsequently, the calculated Do_2 decreased in proportion to the decreases in both CO and PaO_2, as shown.

During tension pneumothorax in the ECMO tension pneumothorax group, increasing intrathoracic volume (as evidenced by increased inferior vena caval pressure) also resulted in decreased venous return, decreased pulse pressure, and decreased mean arterial pressure. Compared with baseline, however, each of the 6 ECMO tension pneumothorax dogs demonstrated the triad of increased PaO_2, decreased peripheral perfusion, and decreased ECMO flow. The PaO_2 increased from 92 ± 7 to 325 ± 20 mm Hg ($p < 0.05$) (Fig 2). The decrease in peripheral perfusion was evidenced by decreased pulse pressure (55 ± 4 to 31 ± 5 mm Hg; $p < 0.05$) (Fig 3) and decreased SvO_2 (71% ± 3% to 22% ± 2% saturation; $p < 0.05$) (Fig 4). When venous return to the ECMO circuit was reduced beyond the amount necessary to sustain ECMO flow at 60 mL/kg/min, the servo-regulated pump stopped, effectively removing the animal from ECMO. At this point (reached at an average of 170 mL/kg of air injected), rapid hemodynamic deterioration was observed in each of the animals (Do_2 decreased from 285 ± 11 to 111 ± 12 mL/min; $p < 0.05$) (Fig 5).

During tension pneumothorax, some consistent changes were observed in both control and ECMO dogs. As illustrated in Figure 1, increasing intrathoracic volume resulted in an increase in inferior vena caval pressure, a decrease in venous return, and subsequently a decrease in both pulse pressure and mean arterial pressure. Heart rate was similar in both groups without major changes throughout the experiment. In the ECMO tension pneumothorax group, CO was supplemented by the nonpulsatile ECMO roller pump, resulting in a consistently greater output than observed in the control animals (820 ± 90 and 420 ± mL/min, respectively; $p < 0.05$). Likewise, the supplemented CO in the ECMO group allowed a greater Do_2 among the ECMO dogs compared with control (231 ± 4 and 131 ± 9 mL/min, respectively; $p < 0.05$). When venous return decreased beyond that necessary to sustain pump flow at 60 mL/kg/min, the servo-regulated pump shut off, thus eliminating the ECMO flow and resulting in a decrease in CO and Do_2 to the level of the control group. The most striking difference between the ECMO and control groups was observed in measurements of PaO_2. In the ECMO tension pneumothorax group, tremendous increases were observed, whereas in the control group, PaO_2 decreased (325 ± 19 and 35 ± 3 mm Hg, respectively; $p < 0.05$).

All 9 dogs survived for the duration of the experiment. Aspiration of the intrathoracic air allowed return to base-

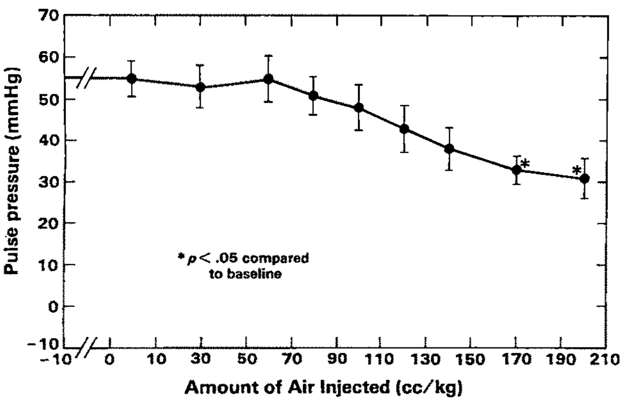

Fig 3. Decline in pulse pressure as tension pneumothorax develops while on extracorporeal membrane oxygenation.

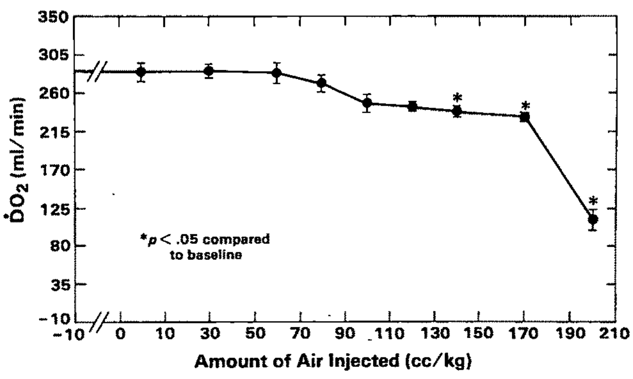

Fig 5. Decline in oxygen delivery (DO_2) as tension pneumothorax develops while on extracorporeal membrane oxygenation.

line values in both control and ECMO dogs (see Fig 1). In the ECMO group, resolution of the tension pneumothorax allowed sufficient venous return to reestablish the ECMO pump flow, resulting in reversal of the triad as ECMO flow increased, PaO_2 decreased, and peripheral perfusion increased, as evidenced by return of both SvO_2 and pulse pressure to baseline values.

Comment

Extracorporeal membrane oxygenation is a technique that has been available for the last 10 years [1, 9–16]. Bartlett and associates [9–12] have reported substantial success with greater than 90% survival in their most recent experience treating meconium aspiration, persistent fetal circulation, infant respiratory distress syndrome, and congenital diaphragmatic hernia.

While the patient is on venoarterial bypass, catastrophic hemodynamic deterioration is unusual. When it occurs, several factors deserve immediate evaluation: proper venous cannula placement, adequate systemic blood volume, and extracorporeal circuit failure. Once these potential problems have been eliminated, one should consider intrathoracic complications that can decrease venous return to the heart and thus decrease ECMO flow.

Tension pneumothorax shows a pathophysiology of increasing intrathoracic pressure and decreasing venous return. During ECMO tension pneumothorax, perfusion is initially maintained by the nonpulsatile flow of the ECMO circuit (as evidenced by a greater Do_2 compared with control [see Fig 1]) before further decreases in venous return result in a decrease in ECMO flow and progressive hemodynamic deterioration. With decreased venous return to the heart, pulmonary blood flow is decreased, the native CO is decreased, and the relative contribution of the extracorporeal circuit to peripheral perfusion is increased.

Because peripheral perfusion is initially maintained by the nonpulsatile flow of the ECMO circuit, the peripheral PaO_2 will increase because of the high oxygen tension of the blood exiting the ECMO membrane lung. Paradoxically, the patient will actually experience decreased peripheral perfusion as evidenced by a decreasing SvO_2. The SvO_2 is monitored continuously during ECMO, and its reduction confirms decreased Do_2 [17]. Therefore, the peripheral PaO_2 will increase while the patient will have decreased peripheral perfusion with a decreased pulse pressure and decreased SvO_2. If the problem is not corrected, progression of tension pneumothorax will result in progressive obstruction of venous return, further decrease in ECMO flow, and further hemodynamic deterioration. In the ECMO tension pneumothorax group, decreases in venous return beyond the amount necessary to sustain ECMO flow at 60 mL/kg/min resulted in effective removal of the animal from ECMO, as the servo-regulated pump stopped to prevent air embolism. At this point, rapid hemodynamic deterioration occurred in all animals as CO and Do_2 fell to levels comparable with control values.

Emergent treatment of tension pneumothorax can be accomplished by aspiration of the intrapleural air to reverse the developing pathophysiology. This treatment was successful in all animals; there was a prompt return to baseline hemodynamics.

The triad of increased PaO_2 and decreased peripheral perfusion (as evidenced by decreased pulse pressure and decreased SvO_2) followed by decreased ECMO flow with progressive hemodynamic deterioration consistently appeared during tension pneumothorax on ECMO. As the use of ECMO for newborn severe respiratory failure increases, physicians must be familiar with life-threatening intrathoracic complications, their presentation, and appropriate treatment strategies.

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Mitral Valve Function After Cryoablation of the Posterior Papillary Muscle in the Dog

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Extensive cryoablation of an arrhythmogenic left ventricular posterior papillary muscle associated with ventricular arrhythmias may affect mitral valve function. We studied the long-term effects of extensive cryoablation of the posterior papillary muscle and its ventricular attachment in 10 dogs. The dogs had hemodynamic, electrophysiological, and angiographic testing 1 month after operation. Seven dogs were then killed, and the hearts were examined at that time. Three dogs had repeat assessments 2 and 3 months after operation before they were killed. At 1 month, left ventricular angiography showed normal mitral valve function in all dogs. Pathological examination revealed that the posterior papillary muscle and its left ventricular attachment were replaced by a discrete dense, fibrous scar. The fibrous process involved the mitral valve in 2 dogs. At 3 months, pathological examination showed a marked fibrous scar with chondroid metaplasia and fibrous involvement of the mitral valve chordae and posterior leaflet in all 3 dogs. We conclude that extensive cryoablation of the posterior papillary muscle is not associated with long-term mitral valve dysfunction, and may be the best surgical technique to ablate an arrhythmogenic papillary muscle.

(Ann Thorac Surg 1989;47:872–6)

Preservation of the left ventricular posterior papillary muscle has been a major limitation to extensive ablation [1, 2] or exclusion [3] of arrhythmogenic tissue for surgical treatment of ventricular arrhythmias. As a consequence, surgical management of ventricular tachycardias associated with posterior left ventricular aneurysms has been less than successful [4, 5].

Preservation of the physiology of the posterior papillary muscle has been advocated on the assumption that an intact contractile papillary muscle is mandatory to provide normal mitral valve function.

We report long-term effects on mitral valve function of extensive cryoablation of the normal left ventricular posterior papillary muscle in 10 dogs at 1 month and in 3 dogs at 3 months of follow-up.

Material and Methods

Functional Anatomy of Papillary Muscles

The mitral valve apparatus includes the following elements, which can be arranged in two groups [6]. The first group comprises the leaflets, the subvalvular membrane (mitral valve annulus), and the chordae. The second group relates to the left ventricle: its cavity configuration and size, its ostium, and the walls of the left ventricle including the papillary muscles.

There are two principal anatomical characteristics of the papillary muscles: (1) they are attached to the intermediate third of the left ventricle and protrude into that third of the cavity; and (2) most of the "papillary muscle" is buried in the left ventricular wall, and the protruding part of the muscle is very short. Because most of the papillary muscle is buried in the left ventricular wall, the physiology of posterior papillary muscle contraction cannot be dissociated from left ventricular contraction.

Experimental Protocol

Ten dogs weighing 19.1 to 25 kg (mean weight, 21.4 kg) were premedicated with intramuscular administration of xylazine (1 mg/kg) and anesthetized with sodium pentobarbital (20 mg/kg). Each dog was intubated and ventilated (Harvard ventilator) with a mixture of nitrous oxide and oxygen. Anesthesia was maintained using 1% to 2% Forane (isoflurane). A Swan-Ganz catheter was introduced through the right jugular vein and an arterial catheter, through the right femoral artery. A urinary catheter was inserted.

The heart was exposed through a left lateral thoracotomy in the fifth intercostal space. The pericardium was longitudinally opened posterior to the left phrenic nerve. The heart was suspended in its pericardial cradle, and the left ventricle, left atrium, and ascending aorta were exposed. Cardiopulmonary bypass (Bentley Bio-5 pediatric bubble oxygenator) was established between the left femoral vein and left jugular vein and the ascending aorta. Normothermic cardiopulmonary bypass was used. The aorta was cross-clamped, and myocardial preservation was achieved using cold crystalloid cardioplegia [7] administered through the aortic root.

The posterior papillary muscle was approached through the mitral valve orifice exposed through a vertical incision in the left atrial appendage (Fig 1). The posterior papillary muscle and its attachments to the left ventricular wall were cryoablated for two minutes using a combined

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endocardial and epicardial application of a cryoprobe (Frigitonics Inc) 1.5 cm in diameter cooled to −60°C (Fig 2). One or two endocardial applications were carried out over the papillary muscle and two or three epicardial applications, over its left ventricular insertion. The clamp occluding the aorta was removed (aortic cross-clamp time, 13 to 26 minutes [mean time, 20 minutes]). The left atrial appendage was closed and subsequently tied at its base. Cardiopulmonary bypass was discontinued (bypass time, 40 to 74 minutes [mean time, 54 minutes]).

Before the chest was closed, three quadripolar plaque electrodes were sutured onto the left ventricle near the cryoablated area and onto the right and left atria for postoperative electrophysiological studies. The wires were placed in a subcutaneous pouch for easy postoperative access. The chest was closed. The dogs were kept under intensive monitoring and treatment until they fully recovered.

All animals were treated in compliance with the recommendations of the Canadian Council on Animal Care and the animal care committee of University Hospital, London, Ontario.

Preoperative and Postoperative Assessment

Before operation, a biplane left ventricular angiogram was obtained using a 7F pigtail catheter introduced through the right femoral artery under mild anesthesia. Segmental left ventricular wall motion was assessed, left ventricular ejection fraction was calculated, and mitral valve competence was graded. Complete hemodynamics were obtained using a Swan-Ganz catheter introduced through the right external jugular vein and a left ventricular and aortic catheter introduced through the right femoral artery. Cardiac output was calculated using the thermodilution technique.

A repeat left ventricular angiogram and complete hemodynamics were obtained in all 10 dogs 1 month after operation. An electrophysiological study was performed using the implanted right atrial, left atrial, and right ventricular plaque electrodes. Basic time intervals were obtained. Ventricular programmed electrical stimulation studies were performed using up to three extra stimuli at two paced cycle lengths (450 and 350 ms).

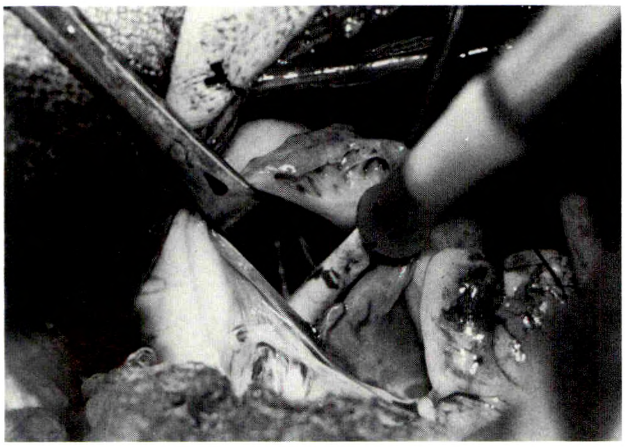

Fig 1. The left atrial appendage has been opened transversely. Under direct vision, a 1.5-cm cryoprobe is positioned on the posterior papillary muscle.

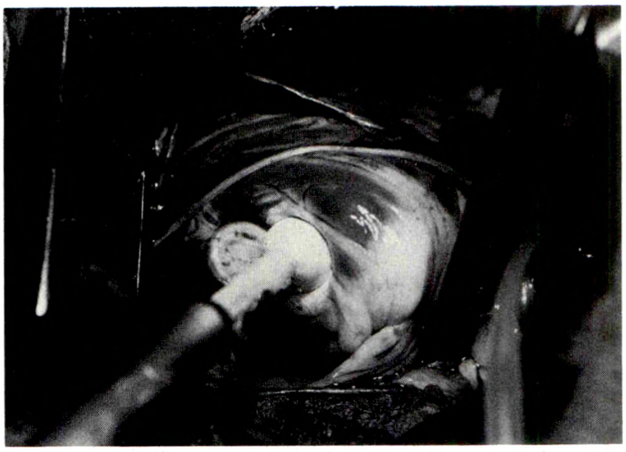

Fig 2. Operative view showing epicardial cryoablation of the left ventricular wall attachment of the posterior papillary muscle.

Seven dogs were killed shortly after the 1-month assessment. The heart was excised for pathological examination. Macroscopic and microscopic examinations of the left ventricular wall, papillary muscle, chordae tendineae, and mitral valve leaflets were carried out.

Two-month and three-month assessments were done in 3 dogs using identical angiographic, hemodynamic, and electrophysiological studies. These dogs were killed after the 3-month assessment, and the hearts were excised and examined.

All experimental data were analyzed for statistical significance by Student's t test for paired data. The results are expressed as the mean ± the standard error of the mean.

Results

One-Month Follow-up in 10 Dogs

Hemodynamic data 1 month postoperatively were within the normal range (Table 1). There was, however, a significant decrease in heart rate and mean aortic pressure, and a significant increase in right ventricular end-diastolic pressure. There was a significant increase in left ventricular ejection fraction from 0.46 ± 0.09 to 0.55 ± 0.06. There was no significant change in cardiac output, mean pulmonary artery pressure, central venous pressure, stroke volume, rate of rise of left ventricular pressure, or rate of rise of right ventricular pressure.

Left ventricular angiography documented normal mitral valve function in all dogs (Fig 3).

Programmed electrophysiological studies did not induce ventricular arrhythmias in any dog.

Pathological examination was done in 7 dogs. At macroscopic examination, there was an easily identifiable and well-delineated scar involving the posterior papillary muscle and its left ventricular attachment (Fig 4). The cryosurgical myocardial necrosis was transmural in all dogs, although the geometry of the scar varied in each animal. The mitral valve was intact in 5 dogs. In 2 dogs,

Table 1. Data at 1-Month Follow-up for 10 Dogs[a]

Variable	Control	1 Month	p Value
Heart rate (beats/min)	108 ± 16	96 ± 15	$p < 0.05$
Pulmonary artery pressure (mm Hg)	11 ± 2	13 ± 4	NS
Pulmonary capillary wedge pressure (mm Hg)	9.5 ± 3	10 ± 4	NS
Aortic pressure (mm Hg)	107 ± 8	84 ± 8	$p < 0.05$
RVEDP (mm Hg)	2.4 ± 1.5	4 ± 1.2	$p < 0.05$
LVEDP (mm Hg)	12 ± 7	11 ± 5	NS
Cardiac output (L/min)	2.37 ± 0.5	2.11 ± 0.5	NS
Stroke volume (mL)	21.9	22	NS
RV dP/dt (mm Hg/s)	259 ± 66	314 ± 121	NS
LV dP/dt (mm Hg/s)	1,847 ± 407	1,926 ± 451	NS
LVEF	0.46 ± 0.09	0.55 ± 0.06	$p < 0.05$

[a] Data are shown as the mean ± the standard error of the mean, except stroke volume, which is the mean only.

LV dP/dt = rate of rise of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; NS = not significant; RV dP/dt = rate of rise of right ventricular pressure; RVEDP = right ventricular end-diastolic pressure.

the posterior leaflet and chordae of the mitral valve were thickened.

Microscopic examination revealed a dense, fibrotic scar. The posterior papillary muscle and its ventricular attachment were replaced by dense connective tissue with collagenous and elastic fibers (Fig 5). In the midportion of the transmural scar, necrotic myocytes were present within the fibrosis. There was almost a line of demarcation between the scar and the normal surrounding myocardium, with sparse fibrotic streaks penetrating the normal myocardium. In 2 dogs, the mitral valve was fibrous. The fibrosis extended from the papillary muscle into the chordae and the posterior leaflet. The epicardial coronary arteries were occluded with fibrosis.

Three-Month Follow-up in 3 Dogs

The hemodynamic data are summarized in Table 2. Hemodynamic variables were within normal limits. Programmed electrophysiological studies did not induce ventricular arrhythmias. Left ventricular angiography showed normal mitral valve competence.

Macroscopic examination demonstrated an area of endocardial fibrosis (3 × 2 cm on average) involving the posterior papillary muscle; its protrusion was identifiable (Fig 6). The fibrosis involved the chordae and the poste-

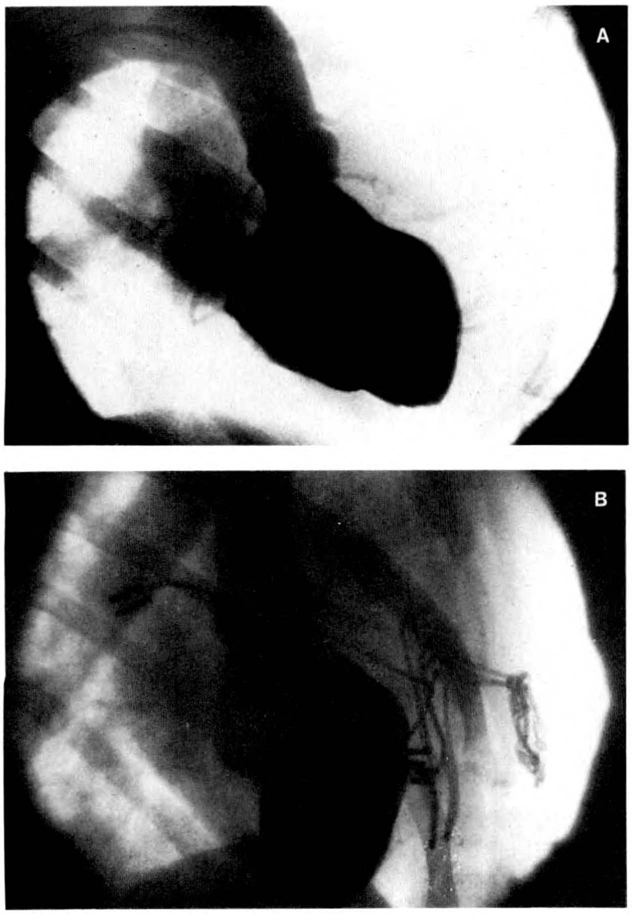

Fig 3. Left ventricular angiograms showed no mitral valve regurgitation (A) preoperatively or (B) 1 month postoperatively.

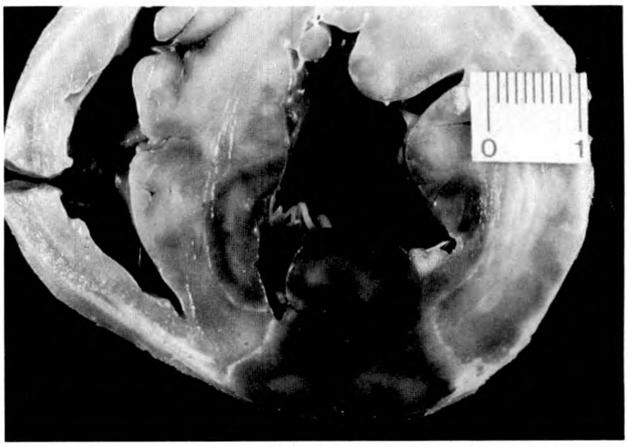

Fig 4. Transection of the left ventricle demonstrating discrete scar from cryoablation of the posterior papillary muscle 4 weeks after operation.

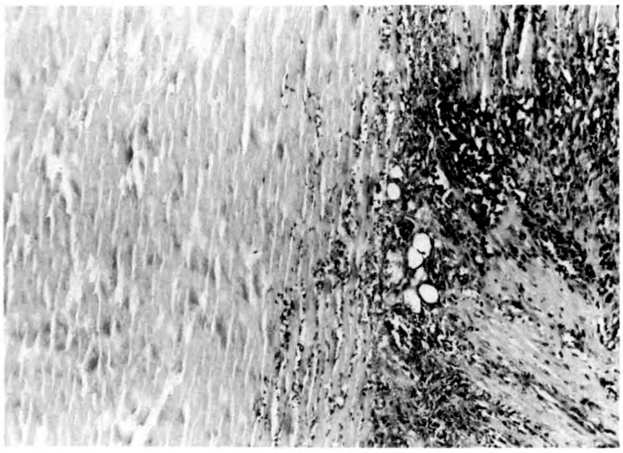

Fig 5. Large area of homogeneous muscular necrosis (left) *surrounded by fibrous and granulation tissue* (right) *(Movat; ×750 before 52% reduction.)*

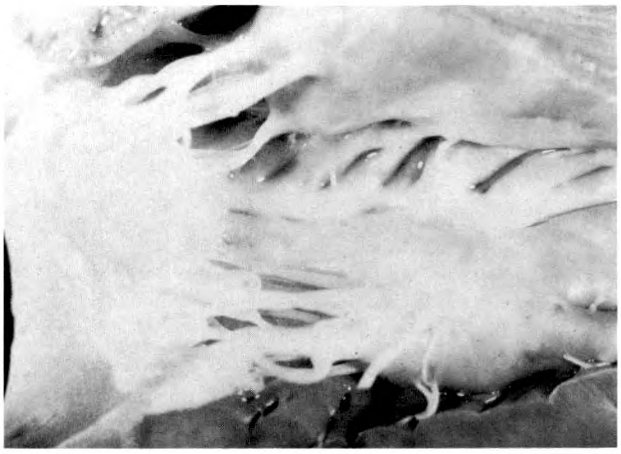

Fig 6. Inferior left ventricular wall 3 months after cryoablation. Endocardial fibrosis covers the posterior papillary muscle and spreads over the posterior chordae and posterior leaflet of the mitral valve.

rior leaflet in all 3 dogs. Microscopic examination revealed a dense scar of connective tissue, with chondroid metaplasia in 2 dogs. There were some scattered necrotic myocytes in the midpart of the scar with chronic inflammation. There was fibrosis of the chordae and the posterior leaflet with focal disappearance of the chordae.

Comment

Discrete extensive cryoablation of the posterior papillary muscle in the dog is feasible and is not associated with long-term mitral valve regurgitation or serious left ventricular dysfunction.

Mitral valve regurgitation due to papillary muscle abnormality is primarily observed in the presence of ischemic heart disease and is caused by elongation or rupture of the papillary muscle [8, 9]. Posteroinferior left ventricular aneurysms are not associated with mitral valve regurgitation in the absence of anatomical disruption of the papillary muscle [10]. Because the role of papillary muscle contraction in mitral valve function is not clear, it was postulated that cryoablation with preservation of the papillary muscle anatomy may not be associated with mitral valve dysfunction.

The cryosurgical myocardial scar has been shown to be dense and composed of fibrotic connective tissue, with no tendency to rupture, dilate, or shrink and without long-term associated ventricular arrhythmias [11, 12]. Our data confirm that the cryosurgical scar preserves the anatomy of the posterior papillary muscle even after 3 months. However, pathological examination demonstrated progressive remodeling of the scar associated with the development of chondroid metaplasia and increased fibrosis of the mitral valve chordae and leaflets.

Because normal canine heart is intrinsically different from the ischemic, infarcted human heart, our results do not necessarily apply to patients with arrhythmogenic inferior scar. We [13] have used extensive cryoablation of

Table 2. Comparison of Follow-up Data for 3 Dogs[a]

Variable	Control	1 Month	2 Months	3 Months
Heart rate (beats/min)	108	107 (NS)	89 (NS)	96 (NS)
Pulmonary artery pressure (mm Hg)	9	16 (NS)	18 (NS)	15 (S)
Pulmonary capillary wedge pressure (mm Hg)	8	12 (NS)	11 (NS)	7 (NS)
Aortic pressure (mm Hg)	105	80 (NS)	90 (NS)	95 (NS)
RVEDP (mm Hg)	1	4 (NS)	3 (NS)	3 (NS)
LVEDP (mm Hg)	8	11 (NS)	10 (NS)	13 (NS)
Cardiac output (L/min)	2.00	2.33 (NS)	2.34 (NS)	2.31 (NS)
Stroke volume (mL)	19.4	21.8 (NS)	26.3 (NS)	24.1 (NS)
RV dP/dt (mm Hg/s)	287	319 (NS)	264 (NS)	250 (NS)
LV dP/dt (mm Hg/s)	1,493	2,153 (NS)	1,627 (NS)	1,927 (NS)
LVEF	0.44	0.50 (S)	0.50 (NS)	0.39 (S)

[a] Data are shown as the mean.

LV dP/dt = rate of rise of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; NS = not significant compared with control value; RV dP/dt = rate of rise of right ventricular pressure; RVEDP = right ventricular end-diastolic pressure; S = significant compared with control value.

the posterior papillary muscle in patients with a posteroinferior left ventricular aneurysm with good results. Similar improved surgical results after cryosurgical ablation for ventricular arrhythmia associated with a posterior left ventricular scar have been reported [14, 15]. We have successfully used extensive cryoablation of the posterior papillary muscle in a patient with ventricular arrhythmia originating from a "normal" posterior papillary muscle without producing mitral valve dysfunction.

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Surgical Management of Aortopulmonary Septal Defect

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Fourteen patients with malseptation of the aortopulmonary trunk underwent operative repair from 1978 to 1988. Age ranged from 1 year to 35 years (mean age, 9.6 years). Five patients had type I, 6 had type II, and 3 had type III lesions. The hemodynamic disturbance in all patients was the consequence of a large left-to-right shunt (mean pulmonary/systemic flow ratio, 2.38:1) with increased pulmonary vascular resistance (mean value, 4.47 units/m^2). Our initial surgical experience with closure under cardiopulmonary bypass through the transaortic route in 3 patients and the transpulmonary approach in two patients resulted in 3 deaths. In the 9 subsequent patients, division and repair of the defect in the great vessels yielded uniformly good results. During follow-up, which ranged from 3 months to 2 years, all 11 survivors had good clinical improvement and none showed residual defects on restudy. Pulmonary artery pressure and pulmonary vascular resistance decreased in all patients except 1.

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Aortopulmonary septal defect is a rare anomaly consisting of a windowlike communication between the aorta and pulmonary artery distal to the level of the semilunar valves. The defect is believed to result from incomplete fusion of the right and left conotruncal ridges above the level of the semilunar valves. According to the classification of Mori and colleagues [1], type I defects occur between the ascending aorta and the main pulmonary artery just above the sinus of Valsalva; type II defects are located between the ascending aorta and the junction of the right pulmonary artery and the main pulmonary artery; and type III defects are a combination of types I and II and involve the entire length of the pulmonary trunk from immediately above both semilunar valves to the level of the pulmonary bifurcation and the proximal portion of the right pulmonary artery.

The major circulatory abnormality of the defect is the direct shunting of blood from the aorta into the pulmonary arteries with severe pulmonary hypertension and early onset of pulmonary vascular disease. The prognosis for patients with aortopulmonary septal defect is uniformly poor unless surgical repair is carried out in early childhood.

In this report, we present our experience with the surgical repair of aortopulmonary septal defect in 14 patients who were seen at our institute from 1978 to 1988.

Material and Methods

Patient Population

Fourteen patients with aortopulmonary septal defect were seen from 1978 to 1988. The age range is given in Table 1. Eight were male, and 6 were female.

All patients were seen with a history of recurrent chest infections, and 5 patients also complained of exertional dyspnea. Three patients had been referred for examination after a futile exploration elsewhere for patent ductus arteriosus. One patient had associated patent ductus arteriosus. Clinical examination showed signs of congestive heart failure in 3 patients and evidence of cardiomegaly and severe pulmonary hypertension in all 14 patients. The electrocardiogram revealed left ventricular hypertrophy in 10 patients and biventricular hypertrophy in 4. The chest roentgenogram revealed a prominent pulmonary artery segment and pulmonary plethora in all patients. Two-dimensional echocardiography could accurately visualize type I lesions but could not always distinguish type II lesions from patent ductus arteriosus.

Cardiac catheterization in all patients demonstrated a large left-to-right shunt (pulmonary/systemic flow ratio, 2.38 ± 0.23 [mean ± standard error of the mean]), severely elevated pulmonary artery pressure (77.3 ± 8.9 mm Hg), and increased pulmonary vascular resistance (4.47 ± 0.88 units/m^2). Cardiac angiography showed a type I defect in 5 patients, a type II defect in 6 patients, and a type III defect in 3 patients.

Surgical Management

Eleven patients underwent surgical repair of the defect with standard cardiopulmonary bypass, moderate hypothermia, and cold cardioplegic arrest of the heart. Pro-

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Table 1. Distribution of Patients by Age

Age (yr)	No. of Patients
0–1	1
2–5	3
6–10	6
11–20	1
21–30	2
31–40	1

found hypothermia with total circulatory arrest was employed in 3 patients because at operation, the defect was noted to be so distal as to preclude aortic clamping and necessitate occlusion of the brachiocephalic and carotid arteries.

In our early experience, the defect was closed with a patch through the transpulmonary route in 2 patients and through the transaortic approach in 3 patients. Two of these 5 patients could not be weaned from bypass, and 1 died of respiratory insufficiency during the postoperative period. Exposure of the defects through the transluminal approach was generally unsatisfactory and particularly difficult for distally placed defects. In type I lesions, the suture closure from within the lumen could also endanger the left coronary artery, which courses in close proximity to the defect. Therefore, in all subsequent patients, we opted for division and patch closure of the communication regardless of its proximal or distal location.

In the revised technique, standard cardiopulmonary bypass was instituted with bicaval and aortic cannulation in patients with a type I defect and bicaval and femoral artery cannulation in those with a type II or III defect. The right and left pulmonary arteries were temporarily occluded on the commencement of bypass, and the systemic temperature was lowered to 25°C. The aorta was cross-clamped above the level of the defect, and cold crystalloid cardioplegic solution was injected into the aortic root. A vent was introduced through the right superior pulmonary vein, and a vertical incision was made over the anterior wall of type I lesions that could be easily identified. The incision was extended circumferentially along the margins of the defect with care taken to keep strictly to the vessel wall. In 1 patient, the defects in the aorta and pulmonary artery were closed directly, but another patient with a type I lesion required patch closure of the aortic defect.

In 4 patients with type II and 3 patients with type III defects, femoral cannulation in preference to aortic cannulation greatly facilitated the cross-clamping of the ascending aorta or cranial vessels and the division and patch repair of the defect under direct vision. In 3 of these 7 patients, the aortopulmonary communication was found at operation to be so distally placed as to make aortic cross-clamping impossible. In these 3 patients, the systemic temperature was reduced to 20°C and circulatory arrest induced before the clamping of the brachiocephalic and left common carotid arteries and the disconnection of the pulmonary artery from the aorta.

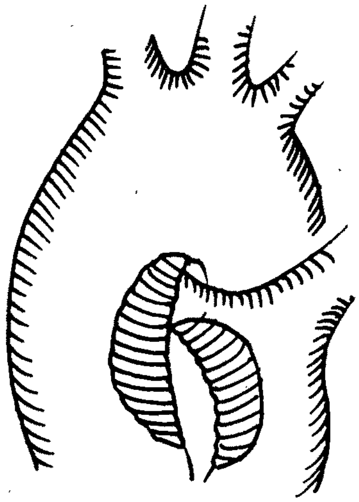

Fig 1. Completed patch repair of defects in the aorta and pulmonary artery.

The large defects in the posteromedial surface of the aorta and anterior surface of the pulmonary artery bifurcation were invariably repaired with plasma-preclotted patches of Dacron (Fig 1). After repair of the aortic opening, the cross-clamp on the aorta or cranial vessels was removed and reperfusion of the brain and heart started when the pulmonary artery opening was repaired with a patch. In this series, occlusion of the aorta or cranial vessels averaged 12 minutes, and cardiopulmonary bypass averaged 78 minutes.

Results

Of the 3 patients who had transaortic repair of the defect, 2 could not be weaned from bypass. One of these patients, who had a type II defect, underwent postmortem examination, which showed that the patch had obstructed part of the origin of the right pulmonary artery and virtually connected the remaining part to the ascending aorta. In the other patient, who had a type I defect, the left coronary artery may have inadvertently been caught in a repair stitch. Of the 2 patients who underwent transpulmonary closure of the defect, 1 died of respiratory insufficiency in the postoperative period. There were no deaths among the 9 subsequent patients who underwent division of the aortopulmonary connection and repair of the resulting defects in the aorta and pulmonary artery.

Follow-up of the 11 survivors ranges from 3 months to 2 years, and is performed on a regular basis. All 11 patients are active and asymptomatic. All underwent recatheterization, which demonstrated an intact repair. Pulmonary artery pressure and pulmonary vascular resistance decreased in all patients except 1, in whom they remained essentially unchanged (Fig 2).

Comment

The first surgical correction of aortopulmonary septal defect was performed by Gross [2], who ligated the defect although he recognized the pitfalls of the ligature tech-

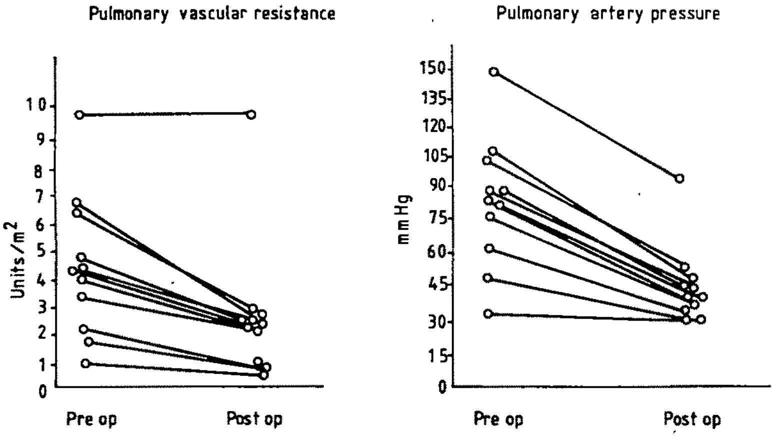

Fig 2. Hemodynamic data before and after repair.

nique. Subsequently, Scott and Sabiston [3] divided and repaired such a defect using partial occlusion clamps. It remained for Cooley and colleagues [4] to employ total cardiopulmonary bypass for the division and repair of aortopulmonary septal defect under direct vision. Wright and associates [5] and others [6–9] have described different techniques for repair, and commented on the difficulties of repairing type II defects in which the communication is more distally located. All reports have emphasized the need for early closure of the defect in view of the progression of pulmonary vascular disease. The repair procedure has been greatly facilitated over the years by the use of cardiopulmonary bypass and, more recently, by profound hypothermia and total circulatory arrest.

Among the reported techniques, the transaortic approach continues to have a role in the repair of type I defects, particularly when they are small. Patch closure of large defects through the transaortic route is less satisfactory because of inadequate exposure and the additional hazard, however small, of catching the left coronary artery in a transluminal stitch. In contrast, an incision in the anterior wall of the communication allows the surgeon to see the defect clearly and direct the incision circumferentially in such a manner as to safeguard the left coronary artery and even borrow from the pulmonary artery wall when necessary.

In our experience, the transpulmonary approach recommended by Putnam and Gross [10] and the transaortic route advocated by others provide even less satisfactory exposure for type II and type III lesions. The autopsy findings in 1 patient with a type II lesion who died after transaortic repair in this series indicated that the patch had obstructed part of the origin of the right pulmonary artery and virtually connected the remaining part to the ascending aorta. This experience of ours does not seem to be unique [8]. The transluminal approach is particularly unsuitable for large distal defects resembling a flow confluence where the ascending and transverse aorta and the pulmonary arteries join. In this situation, disconnection of the pulmonary artery from the aorta and patch repair of individual defects offers a surgical alternative that has little room for error. The option of profound hypothermia and total circulatory arrest has made it possible to extend the use of this technique for even the most distally placed communications.

The operative results and the postoperative status of survivors in our series support continued use of division and repair of aortopulmonary septal defects under cardiopulmonary bypass with or without profound hypothermia and circulatory arrest.

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Disrupted Coronary Artery Caused by Angioplasty: Supportive and Surgical Considerations

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Of 2,859 patients having percutaneous transluminal coronary angioplasty, 201 (7%) underwent emergency coronary artery bypass grafting. Two categories of patients were reviewed. Group 1 consisted of 126 patients of 2,304 who had immediate coronary artery bypass grafting after failed elective percutaneous transluminal coronary angioplasty. Ninety-eight of these patients had angiographic evidence of occlusion of a coronary artery, and 28 had angiographic evidence of coronary artery dissection. Epicardial hemorrhage was observed at operation in 20% (25 patients). Three deaths (2.4%) occurred in group 1, and an average of 3.3 grafts was performed per patient. Group 2 comprised 75 of 555 patients who had unsuccessful attempted percutaneous transluminal coronary angioplasty during an evolving myocardial infarction and required immediate coronary artery bypass grafting. Angiography revealed coronary artery occlusion in 61 patients with dissection in 14. All group 2 patients had evidence of myocardial injury by electrocardiographic and enzymatic (myocardial-specific isoenzyme of creatine kinase) criteria. Three deaths (4%) occurred in this group, and there was an average of 3.4 grafts per patient. Percutaneous transluminal coronary angioplasty is routinely performed without surgical consultation, although an operating room and team are usually available. Supportive techniques include the intraaortic balloon pump and percutaneous cardiopulmonary bypass. In those patients with coronary artery dissection, care must be taken to reestablish the true lumen of the coronary artery. Hemopericardium should be surgically explored and broken guidewires or other foreign bodies or debris removed. From 1979 through 1986, the number of patients requiring emergency coronary artery bypass grafting after percutaneous transluminal coronary angioplasty steadily declined to less than 5%.

(Ann Thorac Surg 1989;47:880–3)

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure used in the catheterization laboratory in the treatment of select patients with coronary artery stenosis [1, 2]. This technique is applied in the case of chronic as well as acute coronary stenosis. From 1979 through 1986, 201 of 2,859 patients undergoing coronary angioplasty required emergency coronary artery revascularization during the immediate periangioplasty period. Of these 201 patients, 126 of 2,304 patients were having elective coronary angioplasty and 75 of 555 patients were having emergency coronary angioplasty for an evolving acute myocardial infarction (MI).

This report describes our supportive and surgical management of these patients.

Material and Methods

The registry of all patients undergoing angioplasty at Mercy Hospital Medical Center, Des Moines, was reviewed. Only the records of patients in whom angioplasty was unsuccessful and who required immediate coronary revascularization were analyzed. Patients who had an unsuccessful angioplasty but did not undergo emergency coronary revascularization were not included in this study. Patients who had had previous coronary artery bypass grafting were not included. In addition, 23 patients (0.8%) seen during the years 1979 through 1986 who died in the catheterization laboratory during angioplasty were excluded.

Two categories of patients were identified. Group 1 included 126 patients who had emergency coronary revascularization immediately after elective PTCA. Group 2 consisted of 75 surgically treated patients who had unsuccessful attempted angioplasty during an evolving MI.

Patients were analyzed as to age, sex, number of vessels attempted at angioplasty, and whether it was a primary or repeat angioplasty. In addition, review was made of the number of bypass grafts per patient, myocardial damage (reflected by enzymatic or electrocardiographic changes), anatomical evidence as to whether or not angioplasty caused coronary artery occlusion or dissection, and operating room recording of observed cardiac trauma resulting from the attempted angioplasty. The mortality rates were determined.

Results

No statistical correlation between age, sex, or the number of vessels attempted at PTCA and the necessity for operative intervention could be found. From 1979 through 1986, there was a significant decrease in the number of

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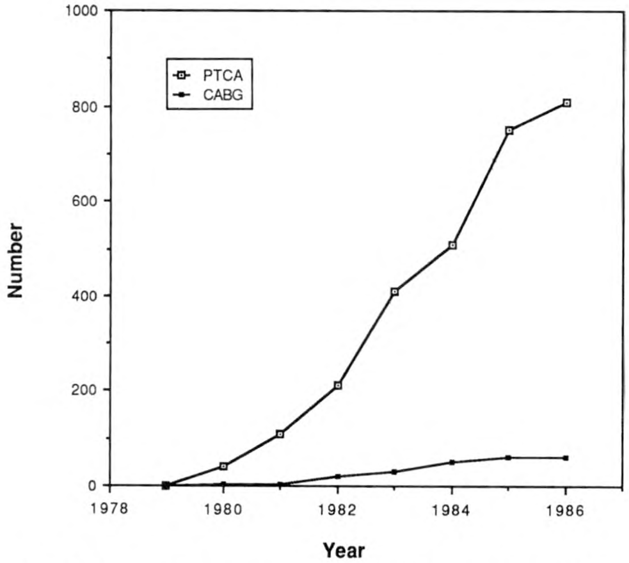

Fig 1. Number of emergency coronary artery bypass grafting (CABG) *procedures as a result of percutaneous transluminal coronary angioplasty* (PTCA) *procedures that failed compared with the number of angioplasty procedures.*

patients undergoing revascularization relative to the number of angioplasties (Fig 1).

All patients were operated on immediately after failure of PTCA, the average time from failed PTCA to complete reperfusion being 2.3 hours. The 126 patients in group 1 had emergency coronary artery revascularization immediately after attempted elective PTCA. A total of 417 coronary artery bypass grafts were done, an average of 3.3 grafts per patient. Postoperatively, 19 patients (15%) demonstrated evidence of a transmural MI by elevation of the myocardial-specific isoenzyme of creatine kinase (greater than 10%) and new Q waves on the electrocardiogram. Other patients showed mild evidence of myocardial injury by slight elevation of the myocardial-specific isoenzyme of creatine kinase (less than 5%) and nonspecific electrocardiographic changes preoperatively to postoperatively. Ventricular function and regional wall motion were preserved in the 107 patients without an MI as measured by postoperative multigated nuclear ventriculography.

Epicardial hemorrhage along the distribution of the PTCA artery was observed at operation in 20% of the patients (25 patients). Ninety-two (73%) of the 126 group 1 patients had debris extracted from the PTCA artery or branches at operation. This debris was essentially atherosclerotic particles showered from the PTCA site downstream or to neighboring vessels. The debris was removed by extracting it with a No. 2 Fogarty catheter or by opening the artery and flushing it with cardioplegic solution.

There were 3 deaths (2.4%) in group 1. In this elective group of 126 patients with unsuccessful PTCA, 22 patients (18%) were having repeat angioplasties. Six patients were undergoing the second PTCA, 10, the third; 4, the fourth; and 2, the fifth.

The 75 group 2 patients with an evolving acute MI and unsuccessful PTCA underwent 255 coronary bypass grafts, an average of 3.4 grafts per patient. Coronary artery occlusion was angiographically present in 63 patients, with dissection in 9. Two patients underwent operation when a guidewire broke off in the left coronary artery (Fig 2) and 2 others, when perforation of a coronary artery resulted in hemopericardium and tamponade (Fig 3). All of these patients showed evidence of myocardial injury by enzymatic and electrocardiographic criteria. There were 3 deaths (4%) in this group.

Overall, 4 patients were supported with percutaneous cardiopulmonary bypass, and 2 survived. Three received cardiopulmonary resuscitation en route to the operating room, and 2 survived. Intraaortic balloon pumps were inserted in 50 of the 201 patients in the catheterization laboratory. "Bailout" catheters were used in 3 patients.

Comment

Grüntzig [1, 2] introduced coronary angioplasty to the clinical practice of cardiology in 1978. Angioplasty is a proven technique for myocardial reperfusion without surgical intervention [3–5]. This approach is useful in select patients with occlusive coronary artery disease. Though originally described for use in patients with single-vessel disease, angioplasty has been extended to patients with multiple-vessel disease [3, 5], stenosed coronary artery bypass grafts [6], unstable angina [7, 8], and acute MI [6, 9].

There are no universally accepted criteria as to which patient subgroup would benefit most from angioplasty intervention compared with revascularization. Not only are there differences in the indication for angioplasty from one institution to another, but there also are differences in patient selection between cardiologists working at the same institution.

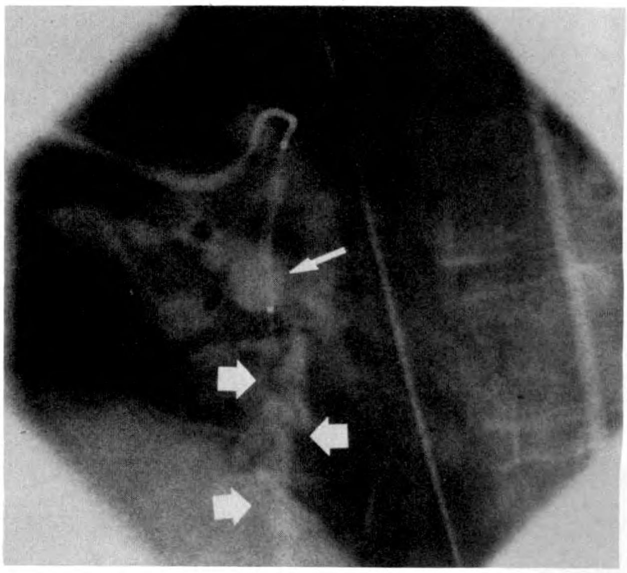

Fig 2. Dissected coronary artery with extravasation of contrast medium (large arrows). *Small arrow points to the percutaneous transluminal coronary angioplasty catheter.*

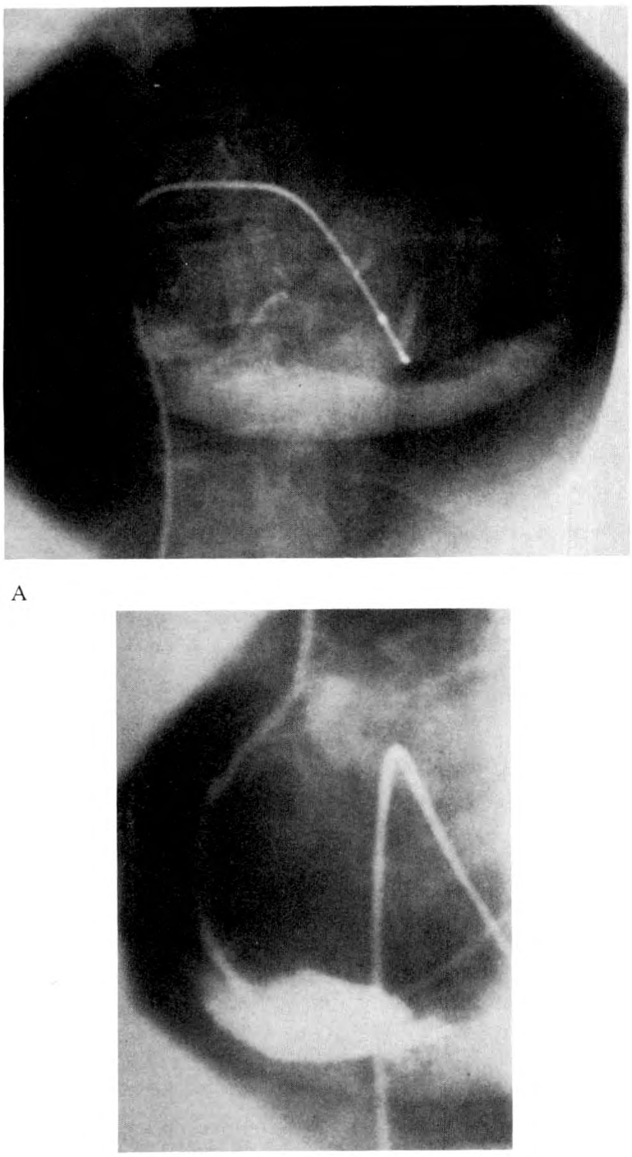

Fig 3. (A) Right anterior oblique and (B) left anterior oblique views. Note hemopericardium (contrast medium) secondary to right coronary artery perforation by percutaneous transluminal coronary angioplasty catheter.

Overall, 7% of our total patient population having coronary angioplasty required emergency operation in the immediate periangioplasty period. Further analysis of these data indicates that of the 2,304 patients having elective angioplasty, 126 (5.5%) had failure of the technique and required emergency operation. This group of 126 patients included 22 (18%) who were having repeat angioplasty. This suggests that repeat angioplasty has a five times greater chance of necessitating emergency revascularization (4% failure rate in our first-time angioplasty population). In group 2, the acute MI group, 75 of 555 patients underwent emergency operation, an incidence of 14%.

It behooves the cardiac surgeon to develop techniques for supporting the patient who experiences mechanical coronary artery disruption with the attendant hemodynamic deterioration until emergency coronary revascularization can be performed. Use of the reperfusion catheter [10], intraaortic balloon pump, and percutaneous cardiopulmonary bypass [11, 12] have proved useful preoperatively. Emergency operation with total revascularization should be performed immediately [13, 14].

In patients with true total coronary artery occlusion, direct bypass of that vessel is relatively uncomplicated technically. The surgeon should attempt to remove any debris found in the PTCA vessel or its branches, and should also be alert to the fact that some arteries that appear occluded on the angiogram are, in fact, occluded secondarily to extensive intimal dissection. In those patients in whom coronary artery dissection has occurred, care must be taken to reestablish the true lumen so that adequate bidirectional reperfusion can be achieved. A technique that we use for finding the true lumen is opening the coronary artery during cardioplegia infusion. When the true lumen is entered, brisk extravasation of cardioplegic fluid occurs. Careful suturing can reapproximate the disrupted walls of that coronary artery to the bypass graft. Endarterectomy has not been necessary, but when present, thrombus or debris is removed.

A careful search for embolic debris in secondary branches of the disrupted vessel must also be performed. When found, it has been our policy to remove this debris by direct arteriotomy followed by bypass of that branch. Repair and bypass was not possible in 1 patient with extensive arterial wall disruption in a large obtuse marginal circumflex coronary artery. Foreign bodies such as broken wires or catheters should be removed and myocardial perforations repaired.

Although the precise role of coronary angioplasty in the treatment of coronary artery disease has yet to be defined, it has become a useful tool in the treatment of select patients with coronary artery occlusive disease. In our opinion, it has replaced medical therapy to a large extent, and thus precisely defined the surgical candidate: a patient with symptomatic coronary artery lesions not amenable to PTCA or a patient in whom PTCA therapy has failed (see Fig 2).

Percutaneous transluminal coronary angioplasty is generally safe, but procedural complications can occur. We believe standby of a surgical team is generally unnecessary, although surgical support should be readily available when PTCA is performed.

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REVIEW OF RECENT BOOKS

Progress in Critical Care Medicine. Volume 3. Critical Care Cardiology

Series Editor, Walter H. Massion
Volume Editor, Jeffrey L. Anderson
New York, Karger, 1988
259 pp, illustrated

Reviewed by Julie A. Swain, MD

This monograph is one in a series on critical care medicine and covers the spectrum of cardiological care in the acute setting, including the pharmacological, mechanical, and surgical treatment of adult heart disease. The authors are primarily from the Universities of Utah and Michigan.

The nine chapters in this text broadly outline the basic principles of care as well as new advances in the field. The two most comprehensive chapters cover thrombolytic therapy and arrhythmia treatment. All commonly used thrombolytic drugs as well as newer agents (tPA, APSAC, prourokinase) are fully reviewed. Antiplatelet therapy is only briefly mentioned. The discussion of antiarrhythmic therapy is an excellent complete review of the uses and complications of these compounds.

The indications for, and short-term and long-term results of, percutaneous transluminal coronary angioplasty are covered well. Cardiac imaging by echo, nuclear, computer-assisted tomographic, and nuclear magnetic resonance scanning is outlined and new developments are discussed. The role of surgical treatment in acute care is only superficially discussed and no mention is made of percutaneous cardiopulmonary bypass.

The chapters are well-referenced and provide a basis for further reading in the field. This monograph will be most useful for general surgical and medical residents, medical students, and nurses, as well as physicians in noncardiac fields.

Bethesda, MD

Incidence of Atherosclerosis in the Internal Mammary Artery

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The long-term patency of the internal mammary artery (IMA) graft is better than that of the saphenous vein graft in coronary bypass procedures. The better patency is thought to be due in part to a relatively low incidence of atherosclerosis in the IMA. In the present study, the incidence of atherosclerosis in the IMA was evaluated in a consecutive Finnish autopsy series of 160 patients. Forty-five patients (28%) had marked occlusion in some coronary arteries as well as a history of angina pectoris. Only 5 (3.1%) of the 160 patients had notable stenosis in the IMA. Three of these 5 patients did not have coronary heart disease. Macroscopic or microscopic signs of atherosclerosis were found in 12.4% of 314 IMAs. We conclude that the low incidence of atherosclerosis in the IMAs in our study is due to their good resistance to the sclerotic process, although the incidence of ischemic heart diseases in Finland is among the highest in the world.

(Ann Thorac Surg 1989;47:884–6)

The saphenous vein graft has been the most popular graft material for myocardial revascularization. The problem with it is the high rate of postoperative occlusion, which is most often due to progressive fibrous or fibromuscular intimal hyperplasia [1–4]. These atherosclerotic changes are more rare in grafts made with the internal mammary artery (IMA) [5, 6]. Currently, the IMA is generally used for coronary artery bypass grafting. The patency rate of this graft is better than that of saphenous vein grafts [7–10].

Finland has among the highest morbidity and mortality rates for coronary heart disease (CHD) in the world [11, 12]. The purpose of this study was to ascertain the incidence of atherosclerosis in the IMA of Finnish patients with or without signs or symptoms of CHD.

Material and Methods

A total of 314 IMAs were evaluated. They were obtained during 160 consecutive postmortem examinations performed in the University Central Hospital of Tampere between January 1 and February 28, 1988. Ninety-eight of the autopsies were medicolegal autopsies of patients who died accidentally, and the remaining 62 involved patients who had died in Tampere University Hospital. The mean age of the patients was 63 years (range, 20 to 94 years). There were 112 men (70%) and 48 women (30%).

Both of the IMAs were studied. Two IMAs were missing because they had been used in coronary bypass procedures, and 4 IMAs had been destroyed accidentally. For light microscopic examination, 4-cm-long pieces were cut at the level of the second rib. Both IMAs were then freed from the inner surface of the thorax; they were opened and washed with cold water. Macroscopic estimations of the extent of the atherosclerotic lesions were done by a subjective evaluation on a scale of 0 to 3: 0 = normal; 1 = fatty streak; 2 = fibrous plaques; and 3 = obstruction. Intimal thickening as a percentage of the luminal diameter was studied. The surface areas of the IMAs were also graded. The area of intima covered by each type of lesion was estimated as a percentage of the total intimal area of the longitudinally opened artery.

The IMA segments were fixed in formalin, embedded in paraffin blocks, and sectioned. Sections were stained with Masson's trichrome stain according to standard procedures. The atherosclerotic features of the lumen and the thickness of the intima were measured using the MOP 3 image-analysis system (Reichert-Jung, Eching, Federal Republic of Germany).

The intima was defined as the distance from the lumen to the internal elastic lamella at the area of greatest intimal thickness (Fig 1) [5]. The interobservation correlation of this measure was 0.98. In addition, 12 samples of both IMAs from 10 medicolegal autopsy subjects were taken for determining the intimal thickness of the artery.

The presence of risk factors associated with the development of atherosclerosis, including hypertension, diabetes mellitus, cigarette smoking, and obesity, was derived from clinical records. Body weight (kilograms) and height (meters) were measured at autopsy, and body mass index (weight divided by the square of the height) was calculated as an indicator of relative body weight. History of CHD was also recorded.

Statistical analyses were made using the test of compliance and two-way analysis of variance. A p value of less than 0.05 was considered significant.

Results

Of the 314 IMAs, only 1 was found to have intimal thickening of greater than 50% of the diameter of the

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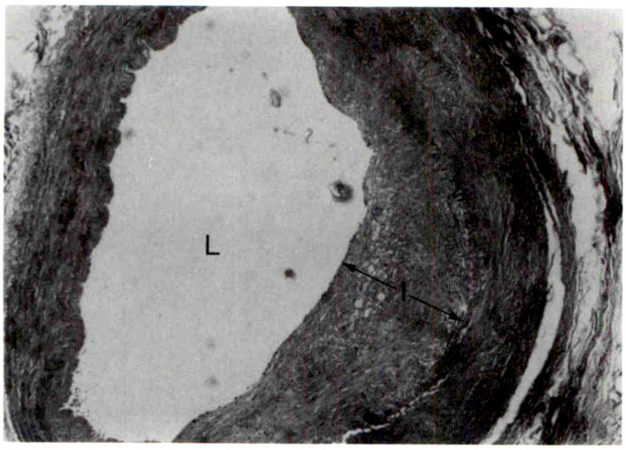

Fig 1. Cross section of internal mammary artery. (Masson's trichrome stain; ×30 before 54% reduction.) (I = intima with atherosclerotic alterations; L = lumen.)

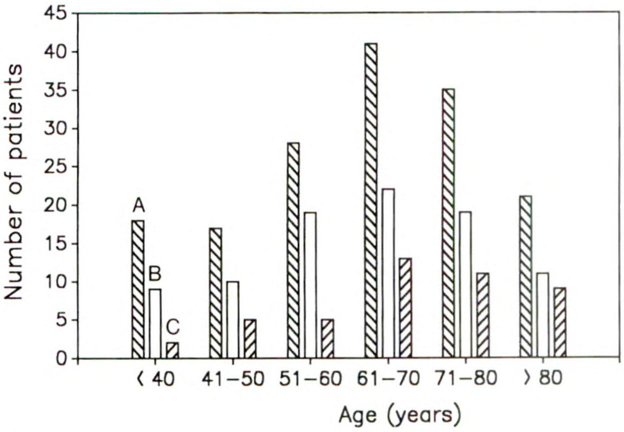

Fig 2. Number of patients by age and incidence of fatty streaks or plaques and obstructions in coronary arteries. (A = total number of patients; B = number of patients with fatty streaks or plaques; C = number of patients with obstructions.)

lumen. In 7, intimal thickening was 25% to 50%. In the remaining 306 arteries, the thickness of the intima was less than 25% of the lumen and therefore was not considered flow limiting. Macroscopic atherosclerotic lesions were found in 39 IMAs from 23 patients (Table 1). In only 1 was the area of the lesion 25% of the luminal surface area of the IMA; in 1, 20%; in 7, 15%; in 7, 12%; in 11, 10%; and in 12, 5%.

Fibrotic plaques were present in the ostium of the IMA in 18 patients. Three patients had plaques in the ostium of both IMAs; in 1, these caused marked stenosis in the ostium of the left IMA. Two other patients had marked stenosis only in the ostium of the left IMA and 2, in the right IMA. The remaining plaques did not cause notable stenosis.

There were 45 patients with CHD (one or more total or almost total occlusions of the coronary arteries), and all of them had signs of angina pectoris according to the clinical history. The number of patients by age in decades and the macroscopic atherosclerotic alterations in the coronary arteries and in the IMA are shown in Figures 2 and 3, respectively. There was no correlation between major macroscopic atherosclerotic alterations in the IMA and CHD (compliance = 0.19). Also, there was no correlation between age and thickness of the intima of the IMA (compliance = 0.19). Three of the 5 patients with marked ostial stenosis did not have CHD. The only patient with intimal thickening of greater than 50% did not have either CHD or angina pectoris.

Of the known risk factors associated with the development of atherosclerosis, only hypertension correlated with the intimal thickness ($p < 0.025$); diabetes alone and diabetes with hypertension did not. The IMAs of smokers did not differ from those of nonsmokers or former smokers, and the body mass index did not correlate with the intimal thickness of the IMA. Both of these factors correlated well with CHD in the present material (data not shown).

Atherosclerosis is a segmental disease. In the 12 IMAs studied, the thickness of the intima varied over the whole length, although not markedly.

Comment

Internal mammary artery grafts are superior to other types of conduits in terms of both long-term patency and late clinical outcome [7, 8, 13, 14]. We do not know the

Table 1. Macroscopic Findings of Atherosclerosis in Samples From 314 Internal Mammary Arteries

Finding	No. of Arteries[a]
Normal	275 (87.6)
Fatty streak	37 (11.8)
Plaque	2 (0.6)
Obstruction	0 (0)

[a] Numbers in parentheses are percentages.

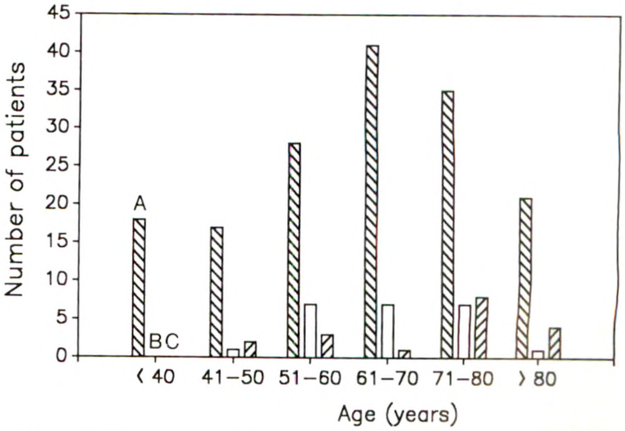

Fig 3. Number of patients by age and number of patients with atherosclerotic alterations in 1 or both internal mammary arteries (IMAs). No patient in this series had obstruction of the IMA. (A = total number of patients; B = fatty streaks; C = plaques.)

basic mechanism whereby the IMA is resistant to atherosclerosis. In our study, there was major obstruction due to fibrous plaques in 6 IMAs (1.9%) from 5 patients (3.1%). Previous studies also showed a low incidence of atherosclerosis in the IMA: Kay and associates [5], 4.2%; and Mestres and co-workers [15], 5%. Although the mortality due to all cardiovascular diseases and particularly ischemic heart diseases is very high in Finland, the incidence of stenosing atherosclerotic plaques is lower than elsewhere. It was surprising that patients with CHD had no more marked atherosclerosis in the IMA than other patients.

The extent of atherosclerotic alterations in the aorta and coronary arteries increases with age [16, 17]. In our study, obstruction of the coronary arteries increased with age, but there was not a linear positive correlation between age and all atherosclerotic alterations in the coronary arteries. There were no obstructions at all in the IMA, and the intimal thickness of this artery did not increase with age.

It should be kept in mind that autopsy series are selectively biased in various ways. Observations made from them cannot be directly related to the living population. At present, however, we do not have other methods for studying IMAs in vivo.

Of the risk factors of CHD, only hypertension seemed to be also a risk factor for thickening of the IMA intima. Body mass index was not a good predictor of intimal thickness in this study. Donahue and associates [18] have even shown that measurement of the subscapular skinfold is a better predictor of CHD, as it takes central obesity into account. The reasons why the other risk factors do not correlate with the intimal thickness of the IMA are unknown.

This study shows that atherosclerosis in the IMA is rare even in a country with a high risk of CHD and even in patients with CHD. The IMA graft is an excellent conduit because it has a better patency rate than the vein graft. Patients with an IMA graft also have a lower incidence of reoperation [19]. Because 5 patients had substantial ostial stenosis of the IMA, it is necessary to evaluate the IMA by angiography before use.

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Nd:YAG Laser Pleurodesis Through Thoracoscopy: New Curative Therapy in Spontaneous Pneumothorax

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From January 1986 to May 1987, 14 patients with spontaneous pneumothorax were treated in our department with a new endoscopic method using neodymium: yttrium-aluminum-garnet laser photocoagulation through thoracoscopy. The 10 male and 4 female patients ranged in age from 14 to 59 years (mean age, 29 years). In all patients, the procedure was performed under general anesthesia. The thoracoscope was introduced through a 1- to 1.5-cm incision in the anterior axillary line of the fourth intercostal space. The fiber of the laser was advanced through the operative channel of the thoracoscope. In all patients, the bleb (or blebs) detected in the apex of the upper lobe was successfully coagulated with low-power laser pulses. Then the parietal pleura of the first five ribs was partially scarified to achieve pleurodesis. There were no side effects. Thirteen patients were successfully treated without recurrence (maximum follow-up, 29 months). We conclude that this new therapy can play an important role in select patients with spontaneous pneumothorax.

(Ann Thorac Surg 1989;47:887–9)

Spontaneous pneumothorax is a common occurrence, particularly in young people. At present, the etiology and pathogenesis are well established, but disagreement remains on the best mode of therapy. Closed tube thoracostomy is considered the main therapeutic approach in the majority of patients, but this method is usually ineffective in preventing recurrences [1]. The other nonoperative therapies, including chemical pleurodesis using sclerosing agents, have frequently been associated with undesirable side effects, and the success rate is usually low [2]. In light of these findings, the only therapy effective in preventing recurrences is surgical pleural abrasion with resection of the lung lesions.

This report describes a new endoscopic therapy. Use of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser through thoracoscopy allowed us to achieve successful results in 13 patients with spontaneous pneumothorax.

Material and Methods

Only patients with truly spontaneous pneumothorax were accepted into this study. Those with neonatal, neoplastic, traumatic, or iatrogenic pneumothoraces were excluded.

The following procedure was applied in every instance. Approximately six to 12 hours after the diagnosis of pneumothorax was made, the patient underwent endoscopic treatment. After premedication with intramuscular administration of atropine, 0.50 mg, and diazepam, 10 mg, the patient underwent operation.

Thoracoscopy was performed under general intubation anesthesia with the patient in the normal supine position. We employed a 7-mm thoracoscope including a 7-mm wide Trocart and two telescopes, direct 180 degrees and lateral 90 degrees (modified Storz). The Trocart was inserted into the fourth intercostal space through a 1- to 1.5-cm incision on the anterior axillary line. A general view of the lung surface and the parietal pleura was obtained first with the lateral telescope. If thoracoscopy showed large and multiple bullae, the patient was referred for thoracotomy with resection and mechanical pleurodesis. Only patients with blebs with a diameter smaller than 2 to 3 cm were accepted for laser treatment (Fig 1). The sterile fiber of the Nd:YAG laser (MBB 100 W) was advanced through the operative channel of the thoracoscope. Any adhesions present were completely lysed with the laser pulses to permit examination of the entire visceral pleura.

Scarification and carbonization of the pleural surface of the first five ribs were performed using short pulses (0.5 second each) and 40 to 50 W. Scarification and carbonization were obtained by directing the Nd:YAG laser beam at the parietal pleura covering the surface of the rib (to avoid possible damage to the intercostal vessels). The carbonization was extended for 5 to 6 cm. Afterward, the Nd:YAG laser beam was directed toward the bleb. Using lower-power pulses (less than 25 W), the bleb was coagulated and sealed (Fig 2). At the end of the procedure, an Argyle chest drainage tube was positioned through the same incision and the underwater seal connected. After mechanical hyperventilation of the lung, the patient was awakened. Suction of 20 cm H_2O was maintained to aid in reexpansion of the lung. Prophylactic antibiotics were used in all patients.

The duration of anesthesia ranged from 30 to 50 min-

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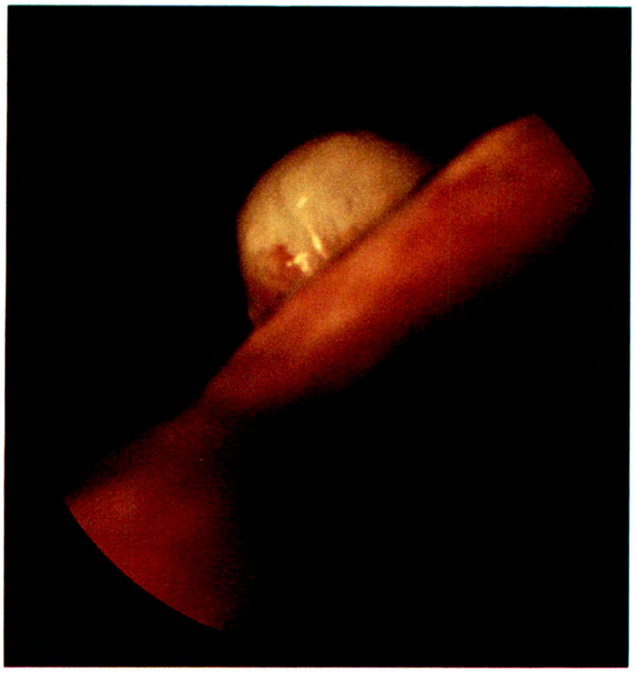

Fig 1. Endoscopic view showing bleb on the apex of the right lung.

utes. The total energy delivered to the patient ranged between 1,500 and 3,600 J (mean energy delivered, 2,600 J).

Follow-up examinations were performed after 1, 6, 12, and 24 months with chest roentgenograms. Minimum follow-up was 14 months.

Results

From January 1986 to May 1987, 33 patients with spontaneous pneumothorax were seen in our department. Fourteen patients from this group were treated with the laser procedure. The 10 male and 4 female patients were between 14 and 59 years old with a mean age of 29 years.

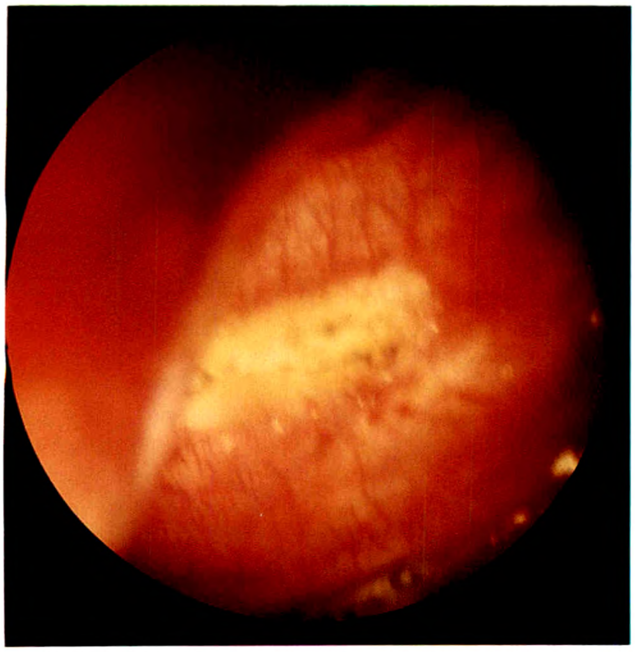

Fig 2. Endoscopic view showing sealing of the bleb after neodymium: yttrium-aluminum-garnet laser phototherapy.

Nine patients were seen with a first episode of pneumothorax and 5 patients, with recurrent pneumothorax. In 11 patients, the pneumothorax was on the right side. The most common symptoms were acute chest pain (92%) and shortness of breath (65%). All patients were hospitalized within 48 hours after the onset of symptoms.

Chest roentgenography was the only radiographic examination performed. It showed total lung collapse in 9 patients and partial collapse (always greater than 30%) in the remaining patients. In 13 patients, postoperative chest roentgenograms demonstrated complete reexpansion of the lung. None of these 13 patients experienced a further episode of pneumothorax during the follow-up of 14 to 29 months. In 1 patient, complete reventilation of the lung was achieved after 48 hours after endoscopy only. All patients tolerated the procedure well, and there were no side effects. In 13 patients, the treatment was successful without complications. Hospitalization ranged from four to six days.

In 11 patients, the chest drainage tube was removed within 48 hours after pleurodesis; 3 patients with persisting air leaks required drainage for four days. One patient was discharged from the hospital after complete reventilation of the lung, but 15 days later, he was readmitted because of recurrence. The chest roentgenogram revealed a lower pneumothorax. At thoracotomy, multiple little blebs, misdiagnosed during pleuroscopy, were detected in the lower lobe. The upper lobe was strongly adherent to the pleural apex on the zone of Nd:YAG laser pleurodesis. In all patients, α_1-antitrypsin values were normal. During the postoperative period, 12 of the 14 patients had a moderate rise in temperature (37.3° to 38.5°C), which resolved in a short time without supplemental therapy.

Comment

Spontaneous pneumothorax in healthy individuals is nearly always due to the rupture of a subpleural bleb or bulla, usually located in the apex of the lung. Although it is commonly agreed and accepted that the first goal of any therapy is to achieve adhesion between the visceral and parietal pleuras, there is continual debate about the timing and the best type of therapy [3, 4]. Closed tube thoracostomy is the easiest and fastest way to obtain quick reventilation of the lung, but this method does not prevent recurrences. At present, the mainstay of surgical therapy is considered to be resection of the blebs and abrasion of the parietal pleura using a dry sponge or cautery. Surgical treatment has a minimal incidence of recurrence, whereas nonoperative procedures have recurrence rates ranging from 30% to 50% [1, 3].

To avoid the potential risk of surgical intervention, many authors have attempted to achieve pleural symphysis using a variety of chemical sclerosing agents. The administration of silver nitrate, talcum powder, tetracycline, or biological glue through the thoracoscope or through chest drainage has been proposed, but the success rate is usually low and the possibility of side effects exists [2, 4–6]. Moreover, none of these methods permit the treatment of lung lesions.

Until now, use of the Nd:YAG laser in thoracic surgery has basically been proposed only for ablative attempts through bronchoscopy in patients with inoperable bronchial cancer [7]. In 1985, LoCicero and associates [8] demonstrated that both the carbon dioxide and the Nd:YAG laser can be used to seal lung air leaks. To the best of our knowledge, ours is the first report in the English-language literature concerning the use of the Nd:YAG laser through a thoracoscope for spontaneous pneumothorax. The Nd:YAG laser energy can be transmitted through a sterile thin plastic fiber that is easily inserted into the operative channel of the thoracoscope. Using pulses of 40 to 50 W, it is possible to accomplish scarification and coagulation of the parietal pleura. With lower energy, it is possible to direct energy to the visceral surface of the lung and to obtain coagulation and retraction of the bleb or blebs.

In our experience, the method presented here shortens the hospitalization time, carries minimal risk, and can be considered a definitive treatment. This new procedure should be considered for use only in patients with little blebs and without great lung involvement. In the case of substantial lung involvement, surgical intervention remains mandatory.

In conclusion, considering the excellent results of this series, we think that Nd:YAG laser pleurodesis through thoracoscopy should be considered the treatment of choice in select patients with spontaneous pneumothorax.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the cardiothoracic operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1991 may begin the recertification process in 1989. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1989. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Physiological Changes During Temporary Occlusion of the Superior Vena Cava in Cynomolgus Monkeys

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To evaluate the physiological changes that occur after temporary occlusion of the superior vena cava, we clamped the vena cava for one hour in 6 cynomolgus monkeys, monkeys with a venous system most resembling that of humans. The data from arterial blood gas analysis, ie, pH, arterial oxygen tension, arterial carbon dioxide tension, and HCO_3^-, were within normal limits during and after occlusion of the superior vena cava. Intracranial pressure was 8.6 ± 0.8 mm Hg (mean ± standard error) before occlusion and rose to 22.1 ± 2.2 mm Hg during clamping. It decreased significantly to 17.7 ± 1.9 mm Hg just before removal of the clamp and recovered to 8.6 ± 0.9 mm Hg after the clamp was removed. Regional cerebral blood flow was 45 ± 9 mL/min/100 g before clamping and decreased to 37 ± 3 mL/min/100 g during clamping. It recovered to 47 ± 5 mL/min/100 g after removal of the clamp. Cerebral perfusion pressure was within the margin of safety during clamping. Histological findings in the brain showed the effect of congestion in 1 monkey, but the change was slight. The electroencephalogram and electrocardiogram showed no abnormalities in this experiment. In conclusion, one-hour clamping of the superior vena cava with the azygos vein ligated was safe in 6 cynomolgus monkeys. We believe that in the clinical setting, one-hour occlusion of the superior vena cava would result in findings similar to those in this study, unless particular complications, such as arteriosclerosis or a cerebrovascular disorder, exist.

(Ann Thorac Surg 1989;47:890–6)

Reconstruction of the superior vena cava (SVC) was first reported in 1954 by Jarvis and Kanar [1] in patients with lung cancer. Since then, expanded polytetrafluoroethylene has successfully been used experimentally in animals [2] and clinically [3]. As long-term patency of the substitutes for the SVC has nearly been assured [4], an increasing number of clinical applications of SVC reconstruction is anticipated. Because the effectiveness of the external [5] or internal [6] SVC shunt is not known, we carried out an animal experiment on the safety of SVC reconstruction with temporary occlusion. We used cynomolgus monkeys because their circulatory system most resembles that of humans. We observed the changes that occurred in intracranial pressure, regional cerebral blood flow, and arterial blood gases after temporary occlusion of the SVC with the azygos vein ligated.

Material and Methods

The 6 cynomolgus monkeys weighed 4.3 to 6.6 kg. The experiments were conducted under general anesthesia with tracheal intubation and regulated respiration using a Harvard respirator. Anesthesia was induced with intramuscular administration of ketamine hydrochloride, 10 mg/kg, followed by an initial dose of sodium pentobarbital, 25 mg/kg intravenously. Anesthesia was maintained with intravenous administration of one third of the initial dose as required.

For monitoring circulation dynamics, cannulation of the femoral artery provided for measurement of systemic arterial pressure; cannulation of the femoral vein, measurement of inferior vena cava pressure; and cannulation of a small branch of the jugular vein or of the axillary vein, measurement of SVC pressure to minimize the effect on the collateral circulation. For the measurement of intracranial pressure, a puncture was made percutaneously through the foramen magnum into the cisterna magna using a 23-gauge spinal needle, which was connected with a polyethylene tube (Clay-Adams PE50; inner diameter, 0.58 mm) to a pressure transducer (Gould P23 ID).

For the measurement of regional cerebral blood flow, an incision was made in the skin 1 cm right of the midline at the midpoint (parietal lobe) between nasion and inion to expose the cranium. Then a hole 5 mm in diameter was made in the cranium to expose the dura mater encephali, into which a needle electrode 0.3 mm in diameter (hydrogen electrode needle model MHD-60; MT Engineering, Japan) was inserted to monitor tissue blood flow at a specific site about 3 mm below the surface of the brain using a tissue blood flow meter (hydrogen-clearance tissue blood flow meter model DHM-3001-01; MT Engineering). Measurement of regional cerebral blood flow (RCBF) was done in accordance with the method of Kohshu and associates [7] by monitoring the clearance of hydrogen gas generated by electrolysis of the local tissues, and the values were computed according to the following equa-

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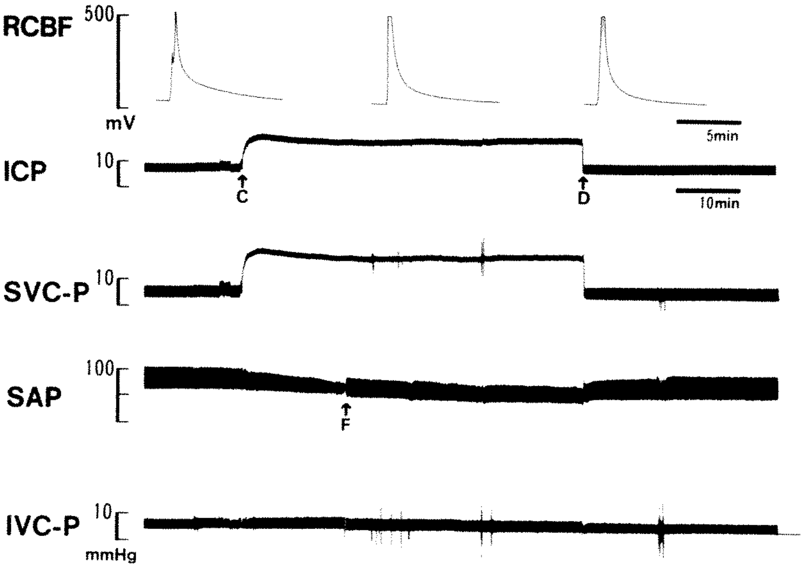

Fig 1. Hemodynamic changes during and after occlusion of the superior vena cava (monkey No. 1). (C = clamping of superior vena cava; D = removal of clamp on superior vena cava; F = flushing with heparinized saline solution; ICP *= intracranial pressure;* IVC-P *= inferior vena cava pressure;* RCBF *= regional cerebral blood flow [hydrogen clearance curve];* SAP *= systemic arterial pressure;* SVC-P *= superior vena cava pressure.)*

tion using the initial slope method for the two-minute clearance curve excluding the initial two-minute period:

$$\text{RCBF (mL/min/100 g)} = 69.3/T_{1/2}$$

where $T_{1/2}$ is half-life (minutes) of the clearance curve.

Concurrently, the electrocardiogram (ECG) and electroencephalogram were recorded on a polygraph. To monitor the electroencephalogram, a corticoelectrode (screw type) was screwed in from a small hole made at the site, which was symmetrical with respect to the site for measuring regional cerebral blood flow. The screw was held firmly in close contact with the dura mater, or a needle electrode was inserted subcutaneously at that point for a monopolar-lead electroencephalogram.

For observation of respiratory function, arterial blood samples were taken as required before, during, and after occlusion of the SVC, and analyzed using a gas analyzer (model ABL-4; Radiometer Inc, Denmark). Ventilation was on room air, and the tidal volume was 100 to 130 mL depending on body weight; the rate of respiration was about ten times per minute. To maintain arterial carbon dioxide tension ($PaCO_2$) at a constant level so as not to affect cerebral blood flow, positive pressure of about 5 cm H_2O (within the physiological limit) was applied at the end of expiration. During and after occlusion of the SVC, constantly regulated respiration was carried out without changing the conditions of ventilation.

Thoracotomy was performed in the right third intercostal space to separate and expose the SVC, and the SVC was occluded using vascular forceps (bulldog clamp; Sklar Inc) after ligation of the azygos vein. During this procedure, 500 IU of heparin sodium was administered intravenously to prevent thrombosis. Temporary occlusion of the SVC was maintained for 60 minutes because the time necessary for the reconstructive procedure is about 30 minutes. Flow in the SVC was restored by releasing the forceps, and for a 30-minute period after removal of the forceps, the respiratory and circulatory conditions were monitored (Fig 1). On closure of the chest, all monitoring devices were removed. After an overnight respiratory control period, the animals were killed, and the brain was resected for histological examination.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

Arterial Blood Gas Analysis

The experiment was initiated on confirmation of stable physiological conditions before temporary occlusion of the SVC. Before occlusion, the arterial blood pH was 7.38 ± 0.01 (mean ± standard error), the $PaCO_2$ was 38.8 ± 0.6 mm Hg, the arterial oxygen tension (PaO_2) was 135 ± 8 mm Hg, and the HCO_3^- was 23.0 ± 0.5 mmol/L. During occlusion of the SVC, pH was 7.40 ± 0.03; $PaCO_2$, 34.8 ± 1.8 mm Hg; PaO_2, 138 ± 9 mm Hg; and HCO_3^-, 21.2 ± 0.7 mmol/L. After release of the clamp, these variables were still within the range of physiological conditions: pH was 7.36 ± 0.02; $PaCO_2$, 39.5 ± 1.2 mm Hg; PaO_2, 141 ± 6 mm Hg; and HCO_3^-, 21.5 ± 0.5 mmol/L. Results of the arterial blood gas analysis showed $PaCO_2$ of 35 to 40 mm Hg was within physiological limits and that pH, PaO_2, and HCO_3^- were nearly constant during and after occlusion of the SVC (Fig 2).

Intracranial Pressure

The intracranial pressure ranged from 8 to 12 mm Hg of systolic pressure, and mean pressure before occlusion was 8.6 ± 0.8 mm Hg. The changes in intracranial pressure after initiation of occlusion are shown in Figure 3. The maximum level of systolic pressure ranged from 25 to 29 mm Hg with a mean of 22.1 ± 2.2 mm Hg. Immediately before release of the clamp at one hour of occlusion, the systolic pressure ranged from 12 to 25 mm Hg with a mean of 17.7 ± 1.9 mm Hg, thus showing a

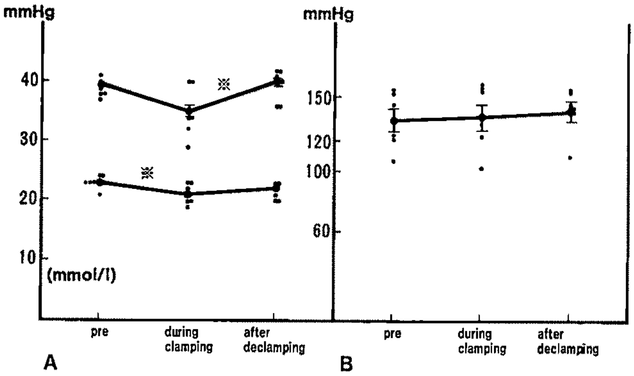

Fig 2. Arterial blood gas analysis: (A) arterial carbon dioxide tension (top) and HCO_3^- (bottom) and (B) arterial oxygen tension. (※ = significant difference [p < 0.05].)

gradual decrease during occlusion. The decrease of 4.4 mm Hg/h was significant ($p < 0.05$). Recovery after release of the clamp was rapid, with all animals returning to baseline (mean, 8.6 ± 0.9 mm Hg).

Pressure in the Superior Vena Cava

The blood pressure in the superior vena cava of the animals was slightly lower than the intracranial pressure, the systolic pressure ranging from 5 to 15 mm Hg with a mean of 5.8 ± 1.2 mm Hg (see Fig 3). As with the intracranial pressure, the maximum level (range, 22 to 39 mm Hg; mean, 29.9 ± 2.6 mm Hg) was reached within a few minutes after initiation of occlusion. Immediately before release of the clamp, the systolic pressure in the superior vena cava ranged from 18 to 37 mm Hg (mean pressure, 25.0 ± 2.7 mm Hg), thus showing a gradual decrease during occlusion (4.9 mm Hg/h). After release of the clamp, recovery was fast, with all animals returning to baseline (mean, 5.9 ± 1.3 mm Hg).

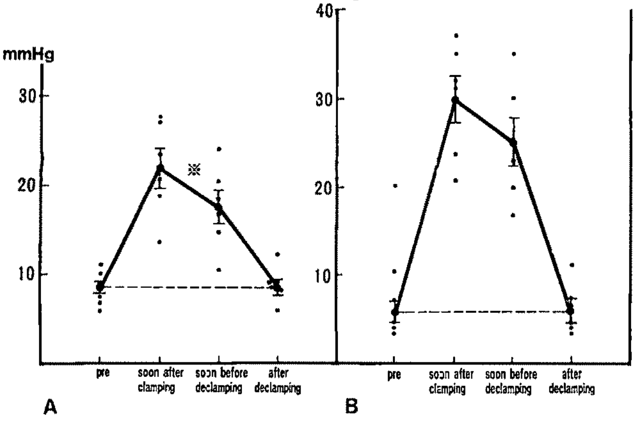

Fig 3. Hemodynamic changes in (A) intracranial pressure and (B) superior vena cava pressure. (※ = significant difference [p < 0.05]).

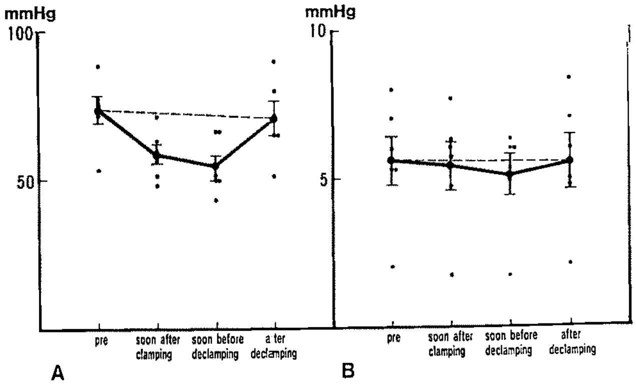

Fig 4. Hemodynamic changes in (A) systemic arterial pressure and (B) inferior vena cava pressure.

Systemic Arterial Pressure

The femoral artery pressure of the monkeys ranged from 80/40 to 125/50 mm Hg with a mean of 73.8 ± 4.7 mm Hg (Fig 4). Both systolic and diastolic pressures decreased immediately after occlusion, and the mean pressure was 58.6 ± 3.4 mm Hg. Immediately before release of the clamp, the pressure ranged from 70/30 to 100/50 mm Hg (mean, 54.7 ± 4.0 mm Hg), showing a mean decrease of 26%. Recovery after release of the clamp was rapid, and at the measurement 30 minutes after release, mean pressure was 70.6 ± 5.5 mm Hg, close to that monitored before occlusion.

Pressure in the Inferior Vena Cava

The systolic pressure in the inferior vena cava of the 6 cynomolgus monkeys ranged from 4 to 12 mm Hg (mean, 5.6 ± 0.8 mm Hg), which was nearly equivalent to the pressure in the SVC (see Fig 4). During and after occlusion, a state of equilibrium was maintained (during occlusion of the SVC, the pressure ranged from 5.4 ± 0.8 to 5.1 ± 0.7 mm Hg; after removal of the clamp, the mean pressure was 5.5 ± 0.9 mm Hg).

Regional Cerebral Blood Flow

Regional cerebral blood flow was monitored at approximately the same site in all animals, ie, 3 mm below the cortex of the parietal lobe. Before occlusion of the SVC, the blood flow ranged from 29 to 90 mL/min/100 g and averaged 45 ± 9 mL/min/100 g (Fig 5). Regional cerebral blood flow was monitored at ten-minute intervals up to 30 minutes after removal of the clamp on the SVC. During the one-hour occlusion period, mean blood flow moni-

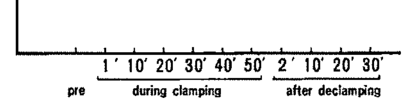

Fig 5. Hemodynamic changes in regional cerebral blood flow.

Table 1. Histological Changes in the Brain

Monkey No.	Frontal Lobe	Basal Ganglia	Hippocampus	Cerebellum
1	No change	No change	No change	No change
2	No change	Some pyknotic neurons in pallidus	Slight pyknotic changes in pyramidal cells in Ammon's horn	No change
3	Small bleeding foci in cortex	Some edema fluid around vessel (Ammon's horn)	Slight pyknotic changes in pyramidal cells in Ammon's horn	No change
4	No change	Some pyknotic neurons in pallidus	No change	No change
5	No change	No change	Slight pyknotic changes in pyramidal cells in Ammon's horn	No change
6	No change	No change	No change	No change

tored at six different times (1 minute and 10, 20, 30, 40, and 50 minutes after initiation of occlusion) was 37 ± 3 mL/m/100 g, which was 18% less than that obtained before occlusion. Regional cerebral blood flow increased with the release of the clamp, and at ten and 20 minutes after release, the blood flow increased transiently to exceed the baseline value, with all 6 animals showing recovery to baseline within the observation period of 30 minutes after release of the clamp. The mean blood flow monitored at four different times (1 minute and 10, 20, and 30 minutes after release of the clamp) was 47 ± 5 mL/min/100 g.

Histological Examination of Brain

After the completion of the experiments with occlusion of the SVC, the chest was closed and all monitoring devices were removed. After the overnight respiratory control period, the animals, all of whom were in stable condition, were killed, and the brain was resected. The sites examined included the right frontal lobe, which is considered to be the dominant hemisphere in the monkey, and the basal ganglia, hippocampus, and cerebellum, which are believed to be sensitive to hypoxia (Table 1). In the frontal lobe, small bleeding foci of venous origin were found in the cortex of only 1 of the 6 animals (Fig 6); no changes were observed in the other 5 monkeys. In the basal ganglia, no changes were detected in 3 animals. Pyknotic neurons were observed in the globus pallidus of 2 monkeys, and perivascular edema and minor bleeding as a consequence of congestion were found in the globus pallidus of 1 animal, but these changes were mild in degree (Fig 7). In the hippocampus, pyknotic changes were observed in a small number of pyramidal cells in Sommer's sector of 3 animals, but it was determined that this change was not associated with the experiment. In all 6 monkeys, Purkinje's cells and the nerve cells of the nucleus dentatus were well preserved. There were no remarkable histological changes caused by the transient occlusion of the SVC, and the animals demonstrated nearly normal brain tissue morphologically.

Electroencephalography

Studies of the minute changes could not be performed because of the effect of other electrical monitoring devices. However, abnormal waves such as slow or sharp waves before or after the initiation of occlusion were not observed in any of the animals.

Electrocardiography

The appearance of abnormal wave patterns of sinus arrhythmia was not noted in any of the animals before, during, or after SVC occlusion.

Comment

The external or internal shunt is generally considered a safe technique for the reconstruction of the SVC. Jarvis and Kanar [1] in their clinical report and Ohara and colleagues [8] in their experimental study with dogs stated that occlusion of the SVC for a short period caused no problems. In fact, the Glenn operation, in which the SVC and the pulmonary artery are anastomosed end to side while the SVC is occluded for a short time, has been safely employed for the treatment of tricuspid atresia [9]. The

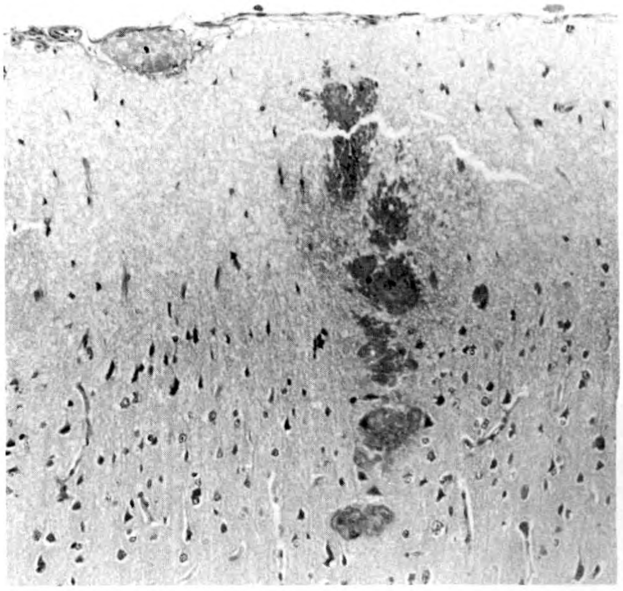

Fig 6. Small bleeding foci in frontal lobe cortex. (Hematoxylin and eosin; ×100 before 35% reduction.)

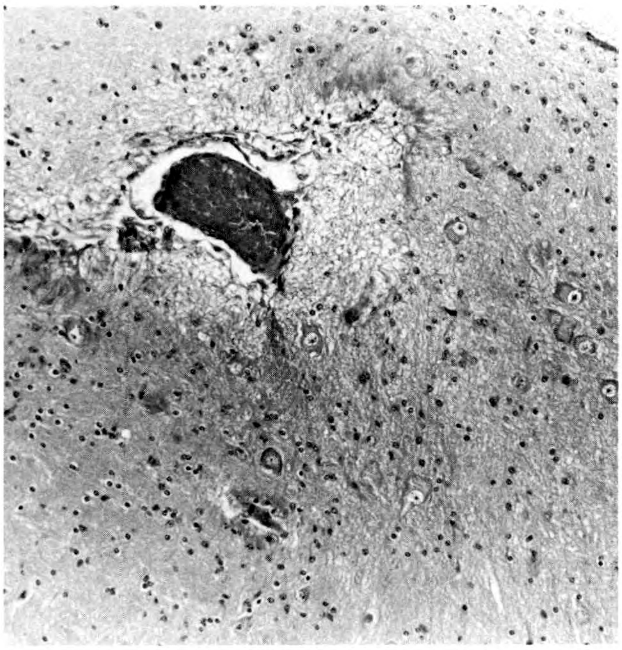

Fig 7. Pooling of edematous fluid surrounds enlarged vessel in pallidus. Neurons show almost normal shape. (Hematoxylin and eosin; ×100 before 39% reduction.)

duration of vascular occlusion needed for reconstruction of the SVC is thought to be about 30 minutes. Therefore, the present animal study was conducted to confirm the safety of SVC reconstruction with temporary occlusion.

In clinical practice, Salsali [5] used an external shunt by inserting a catheter into the right atrium from the left brachiocephalic vein, but did not monitor pressure at all. In their report on internal shunts, Garcia and associates [6] wrote that intravenous pressure was 42 cm H_2O before reconstruction and jumped to 52 cm H_2O as a result of temporary occlusion of the SVC at the time of cannulation and decannulation for placement of the shunt between the SVC and the right atrium. As intravenous pressure during the application of the internal shunt was the same as the preocclusion value (42 cm H_2O), there were no suppressive effects of the shunt.

Moreover, the duration of the operation for SVC reconstruction is more than two hours with the use of a shunt. The effects of the shunt during occlusion of the SVC are greatly restricted by the size of the catheter, resulting in no clinical advantages. In addition, the use of a shunt makes the operative procedures intricate, resulting not only in perioperative adverse effects on patients, but also possibly facilitating blood clot formation because of the enlargement of vascular cut surfaces, which may have undesirable effects on postoperative patency of a substituted vessel. Therefore, we carried out this study using cynomolgus monkeys, which were selected because we wanted to minimize problems with species differences between humans and the experimental animal as much as possible.

In our study, the azygos vein was occluded by ligation before the SVC was occluded because the azygos vein was thought to play an important role in the collateral routes of the SVC. Gomes and Hufnagel [10] reported that the azygos vein was preserved as the collateral route of the SVC in only 14 of 166 patients with SVC syndrome, a finding suggesting the importance of the azygos vein. This vein cannot be preserved in many such patients because a wide surgical margin is required for reconstruction of a seriously affected SVC. As Dale and Scott [11] found that the patency rate was improved with the increase in SVC pressure if the azygos vein was occluded by ligation at the time of SVC reconstruction, occlusion of the azygos vein was thought to be essential to our study.

With reference to anesthesia, some kinds of anesthetics used possibly influence intracranial pressure. For example, occlusion of the jugular vein is sometimes necessary for surgical treatment of malignant tumor in the neck, and poor clinical results are often found when ether anesthesia is employed. This seems to be due to increased intracranial pressure with ether. Sugarbaker [12] clinically measured cerebrospinal fluid pressure, and found that it was almost doubled by ether anesthesia, and that this high pressure was maintained for two to three hours and then gradually decreased to the normal level. These findings indicate that ether anesthesia is inadequate for a study planned to determine the effect of occlusion of the SVC.

In experimental studies of occlusion of the SVC in dogs, Carlson [13], Jarvis and Kanar [1], and Ohara and associates [8] confirmed that occlusion of the SVC distal to the azygos vein was safe. Carlson [13] carried out his studies using ether anesthesia, and found that occlusion of the SVC central to the azygos vein resulted in deaths; the other investigators [1, 8] employed pentobarbital anesthesia and reported that the SVC was safely occluded under occlusion of the azygos vein for less than two hours. These contradictory results are thought to be due to the different anesthetics employed; occlusion of the SVC for a short period is safe if proper anesthetics are selected.

Furthermore, constant respiratory control is essential for measurements of intracranial pressure and cerebral circulation during occlusion of the SVC. Because the arterial carbon dioxide levels influence the cerebral circulatory system, $PaCO_2$ should be maintained at physiological levels [14], about 40 mm Hg, in such experiments. Therefore, previous experiments on occlusion of the SVC were not always performed for clinical application.

In the present study with cynomolgus monkeys, intracranial pressure, the increase of which was considered to be the most serious problem during occlusion of the SVC, was found to be 8.6 mm Hg (mean) before occlusion, 22.1 mm Hg (mean highest) a few minutes after occlusion, and 17.7 mm Hg (mean) immediately before release of the clamp (a significant drop; $p < 0.05$) (see Fig 3). All animals showed rapid recovery after release of the clamp.

Next we determined cerebral perfusion pressure, which is obtained by subtracting intracranial pressure from systemic arterial pressure (all pressures measured in millimeters of mercury). The calculations were made based on mean values. Although the cerebral perfusion pressure needed to maintain the cerebral circulation at the normal level is thought to be 60 mm Hg, the cerebral circulation under such decreased metabolic conditions as hypothermia or administration of barbiturates (as in this study) is thought to be properly maintained unless the cerebral perfusion pressure drops to less than 40 mm Hg [15]. In this study, although cerebral perfusion pressure during occlusion was found to be about 40 mm Hg, the duration of occlusion was short (one hour), and the measurement of regional cerebral blood flow, simultaneously performed, indicated that the decrease in this variable was smaller than that in arterial pressure, ie, about 18%. Zola-Morgan and Micheletti [16] reported that cynomolgus monkeys are very sensitive to pentobarbiturates and require only half the dose used in rhesus monkeys. However, no definite guidelines on the dose of pentobarbital for cynomolgus monkeys have been provided, and we administered pentobarbital in the same dose as in common animal experiments. Thus, our animals tended to show slightly lower systemic arterial pressure as a result of the administration of pentobarbital in a relatively high dose. Therefore, the cerebral perfusion pressure in this study was thought to be within the margin of safety. When the cerebral circulation is judged with only intracranial pressure, 40 mm Hg is considered to be the critical point; our animals showed no problems with this.

McIntire and Sykes [17] described four main collateral routes of the SVC in humans: the internal thoracic, vertebral, azygos, and lateral thoracic venous systems. In our study, the azygos venous system was totally occluded, but the other systems functioned as collateral routes developed. Although macaques do not have exactly the same venous circulatory system as that of humans, Swindler and Wood [18] and Lineback [19] found similar venous systems between these two mammals in their comparative anatomical studies. Therefore, it was thought that the elevation of intracranial pressure in the macaques caused by occlusion of the SVC was reduced mainly by the *vertebral venous system* (where the blood from the sinus venosus and bilateral brachiocephalic veins flows into the intercostal vein, lumbar vein, and sacral vein through the vertebral vein, and then pours into the inferior vena cava; portions of the blood also flow into the internal thoracic vein) as well as the *internal thoracic venous system* (where the blood pours into the inferior vena cava from the internal thoracic vein through the superior epigastric vein, inferior epigastric vein, external iliac vein, and common iliac vein) and the *lateral thoracic venous system* (which is the superficial collateral circulatory system where the blood from the subclavian vein and the axillary vein reaches the lateral thoracic vein and then pours into the femoral vein through the thoracoepigastric vein and the superficial epigastric vein).

As previously reported, we [3] clinically reconstructed the SVC with the aid of temporary occlusion of the SVC, and the patient has survived for more than 7 years (Fig 8). We encountered a similar patient, who has also been in good health for 1 year 2 months. In these 2 patients, the duration of occlusion of the SVC was less than 60 minutes, and neither patient has sequelae. Therefore, we believe that one-hour occlusion of the SVC would clinically show similar results to those found in this study

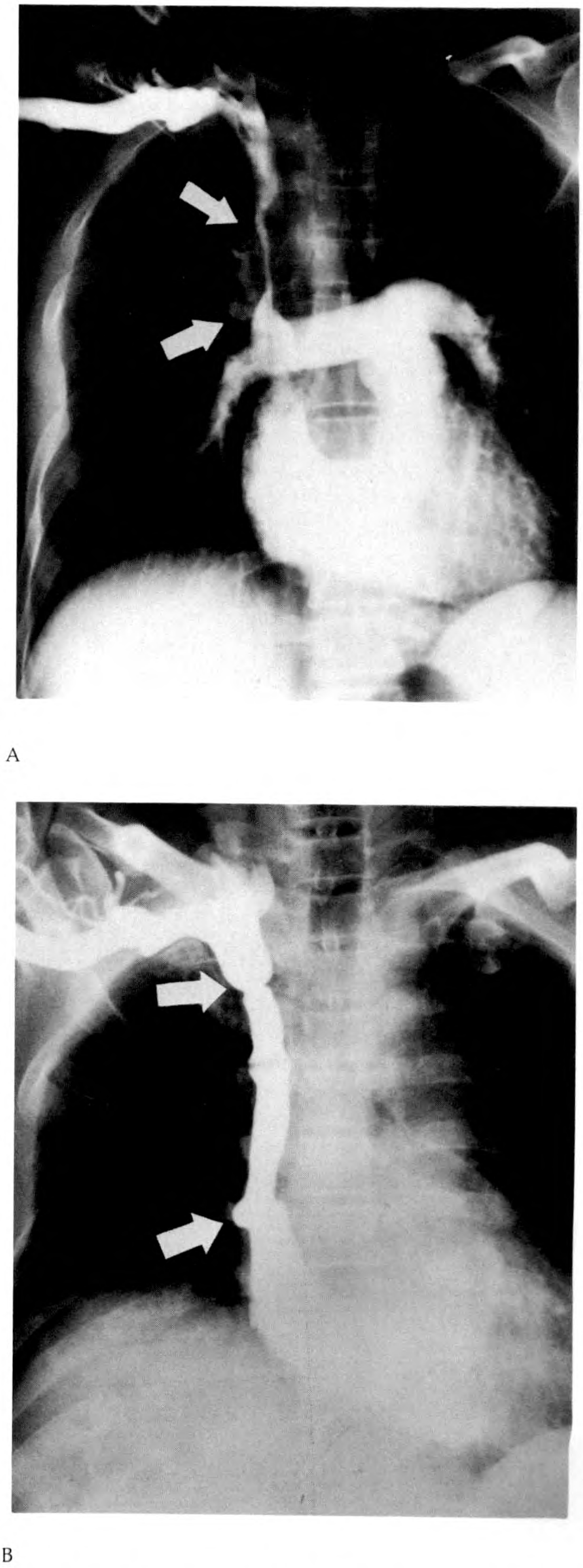

Fig 8. Superior vena cavograms of an invasive thymoma in a 49-year-old man. (A) Arrows *show invasion of the tumor into the superior vena cava. (B) Seven years after operation the expanded polytetrafluoroethylene conduit* (arrows) *is patent.*

unless particular complications, such as arteriosclerosis or a cerebrovascular disorder, exist.

Among the experimental procedures employed in this study, we paid the greatest attention to the management of respiration. The animals were entered into the experiment after arterial blood gas analysis confirmed they could maintain physiological conditions (namely, pH, 7.38; $PaCO_2$, 39 mm Hg; PaO_2, 135 mm Hg; and HCO_3^-, 23 mmol/L {mean values]) under artificial ventilation with a respirator on room air. As for changes during occlusion and after release of the occlusion clamp, $PaCO_2$ remained within the physiological range (mean, 35 mm Hg). On the other hand, PaO_2 showed slight increases, and pH and HCO_3^- remained at almost constant levels. In the t test analysis, HCO_3^- showed a significant decrease from the preocclusion to occlusion period ($p < 0.05$), and $PaCO_2$ demonstrated a significant increase from the occlusion to postocclusion period ($p < 0.05$). The other variables had no significant differences. Although there was a tendency toward metabolic acidosis caused by occlusion, all variables related to metabolism remained within physiological ranges, thus proving the safety of this procedure.

Regional cerebral blood flow was measured at the same place, 3 mm below the cortex of the right parietal lobe. Regional cerebral blood flow before the start of occlusion ranged from 29 to 90 mL/min/100 g. Changes in regional cerebral blood flow were almost identical among the animals; the mean level was found to be 45 mL/min/100 g before occlusion and dropped to 37 mL/min/100 g during occlusion. Therefore, the mean blood flow was decreased by only 18% in comparison with the previous level. After release of the occlusion clamp blood flow quickly recovered. The decrease in regional cerebral blood flow was determined to be less than that in systemic arterial pressure. The findings on the ECG and electroencephalogram exhibited no signs of problems. There were almost no histological changes in the basal ganglia or the hippocampus, both of which are sensitive to hypoxia.

In conclusion, the safety of occlusion of the SVC for one hour was confirmed in 6 cynomolgus monkeys through measurements of intracranial pressure, SVC pressure, systemic arterial pressure, and inferior vena cava pressure. In addition, arterial blood gas analysis, regional cerebral blood flow measurement, electrocardiographic and electroencephalographic recordings, and histological examination of the brain confirm this finding.

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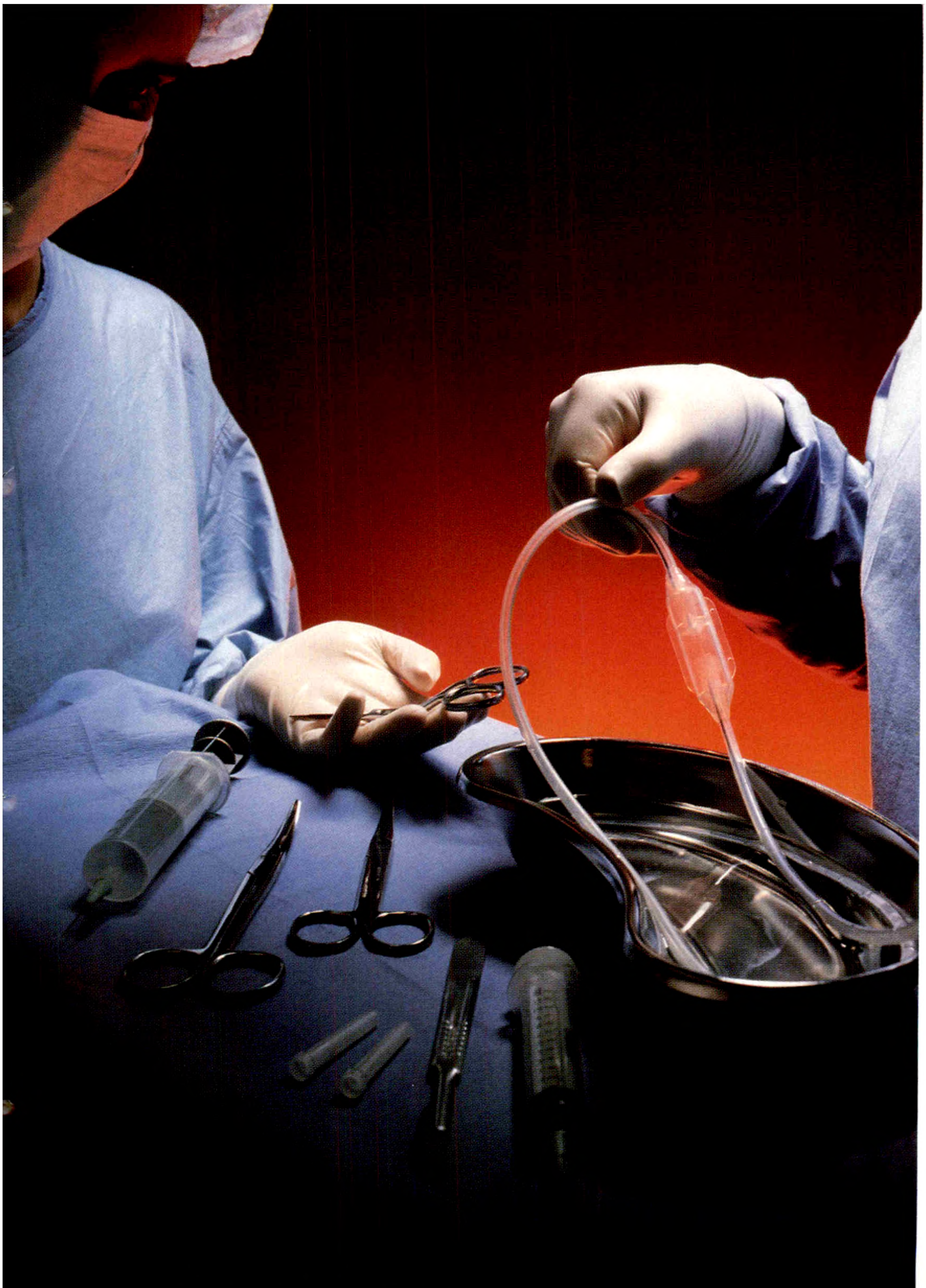

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> **WARNING**
>
> It is recommended that Blenoxane be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.
>
> Pulmonary fibrosis is the most severe toxicity associated with Blenoxane. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.
>
> A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with Blenoxane.

DESCRIPTION

Blenoxane (sterile bleomycin sulfate, U.S.P.) is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of **Streptomyces verticillus.** It is freely soluble in water.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.

ACTION

Although the exact mechanism of action of Blenoxane is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

In mice, high concentrations of Blenoxane are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have been found to have high concentrations of Blenoxane in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of Blenoxane found in bone marrow may be related to high levels of Blenoxane degradative enzymes found in that tissue.

In patients with a creatinine clearance of $>$ 35 mL per minute, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of $<$ 35 mL per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. In humans, 60 to 70% of an administered dose is recovered in the urine as active bleomycin.

INDICATIONS

Blenoxane should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:

Squamous Cell Carcinoma—Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingiva, epiglottis, larynx), skin, penis, cervix, and vulva. The response to Blenoxane is poorer in patients with head and neck cancer previously irradiated.

Lymphomas—Hodgkin's, reticulum cell sarcoma, lymphosarcoma.

Testicular Carcinoma—Embryonal cell, choriocarcinoma, and teratocarcinoma.

CONTRAINDICATIONS

Blenoxane is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

WARNINGS

Patients receiving Blenoxane must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by Blenoxane progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended.

Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of lymphoma patients treated with Blenoxane. Since these usually occur after the first or second dose, careful monitoring is essential after these doses.

Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Usage in Pregnancy: Safe use of Blenoxane in pregnant women has not been established.

ADVERSE REACTIONS

Pulmonary—This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to Blenoxane has been extremely difficult. The earliest symptom associated with Blenoxane pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, Blenoxane-induced pneumonitis produces nonspecific patchy opacities, usually of the lower lung fields. The most common changes in pulmonary function tests are a decrease in total lung volume and a decrease in vital capacity. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to Blenoxane toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific, e.g., similar changes are seen in radiation pneumonitis, pneumocystic pneumonitis.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1 to 2 weeks. If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Recent studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{CO}) during treatment with Blenoxane may be an indicator of subclinical pulmonary toxicity. It is recommended that the DL_{CO} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DL_{CO} falls below 30 to 35% of the pretreatment value.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations than usually would be considered safe. Suggested preventive measures are:

(1) Maintain $FI\ O_2$ at concentrations approximating that of room air (25%) during surgery and the postoperative period.

(2) Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during Blenoxane infusions. Although each patient must be individually evaluated, further courses of Blenoxane do not appear to be contraindicated.

Idiosyncratic Reactions—In approximately 1% of the lymphoma patients treated with Blenoxane, an idiosyncratic reaction, similar to anaphylaxis clinically, has been reported. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose. It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic including volume expansion, pressor agents, antihistamines, and corticosteroids.

Integument and Mucous Membranes—These are the most frequent side effects being reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue Blenoxane therapy in 2% of treated patients because of these toxicities.

Skin toxicity is a relatively late manifestation usually developing in the 2nd and 3rd week of treatment after 150 to 200 units of Blenoxane have been administered and appears to be related to the cumulative dose.

Other—Vascular toxicities coincident with the use of Blenoxane in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with Blenoxane in combination with vinblastine with or without cisplatin or, in a few cases, with Blenoxane as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, Blenoxane, vinblastine, hypomagnesemia, or a combination of any of these factors.

Fever, chills, and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions were reported infrequently.

DOSAGE

Because of the possibility of an anaphylactoid reaction, lymphoma patients should be treated with 2 units or less for the first 2 doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedule is recommended: **Squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, testicular carcinoma**—0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease—0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

Pulmonary toxicity of Blenoxane appears to be dose related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Note: When Blenoxane is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's Disease and testicular tumors is prompt and noted within two weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as three weeks before any improvement is noted.

ADMINISTRATION

Blenoxane may be given by the intramuscular, intravenous, or subcutaneous routes.

Intramuscular or Subcutaneous—Dissolve the contents of a Blenoxane vial in 1 to 5 mL of Sterile Water for Injection, U.S.P., Sodium Chloride for Injection, U.S.P., 5% Dextrose Injection, U.S.P., or Bacteriostatic Water for Injection, U.S.P.

Intravenous—Dissolve the contents of the vial in 5 mL or more of a solution suitable for injection, e.g., physiologic saline or glucose, and administer slowly over a period of ten minutes.

STABILITY

The sterile powder is stable under refrigeration (2°-8°C) and should not be used after the expiration date is reached.

Blenoxane is stable for 24 hours at room temperature in Sodium Chloride or 5% Dextrose Solution.

Blenoxane is stable for 24 hours in 5% Dextrose containing heparin 100 units per mL or 1000 units per mL.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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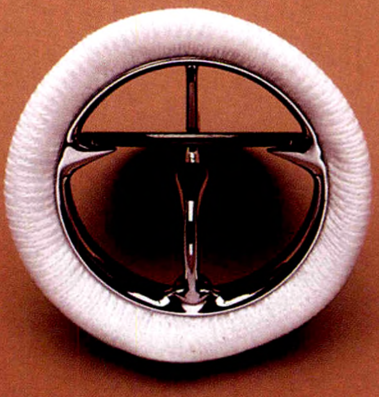

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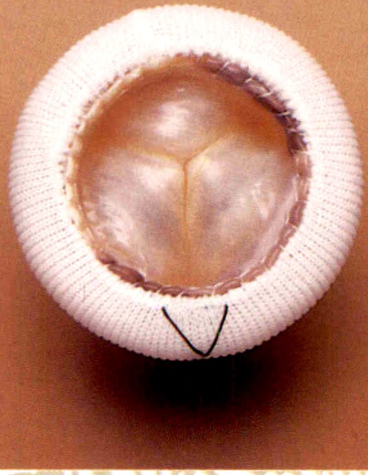

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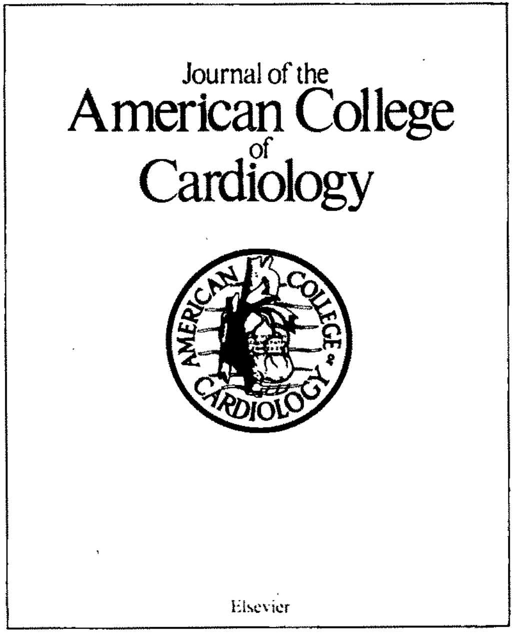

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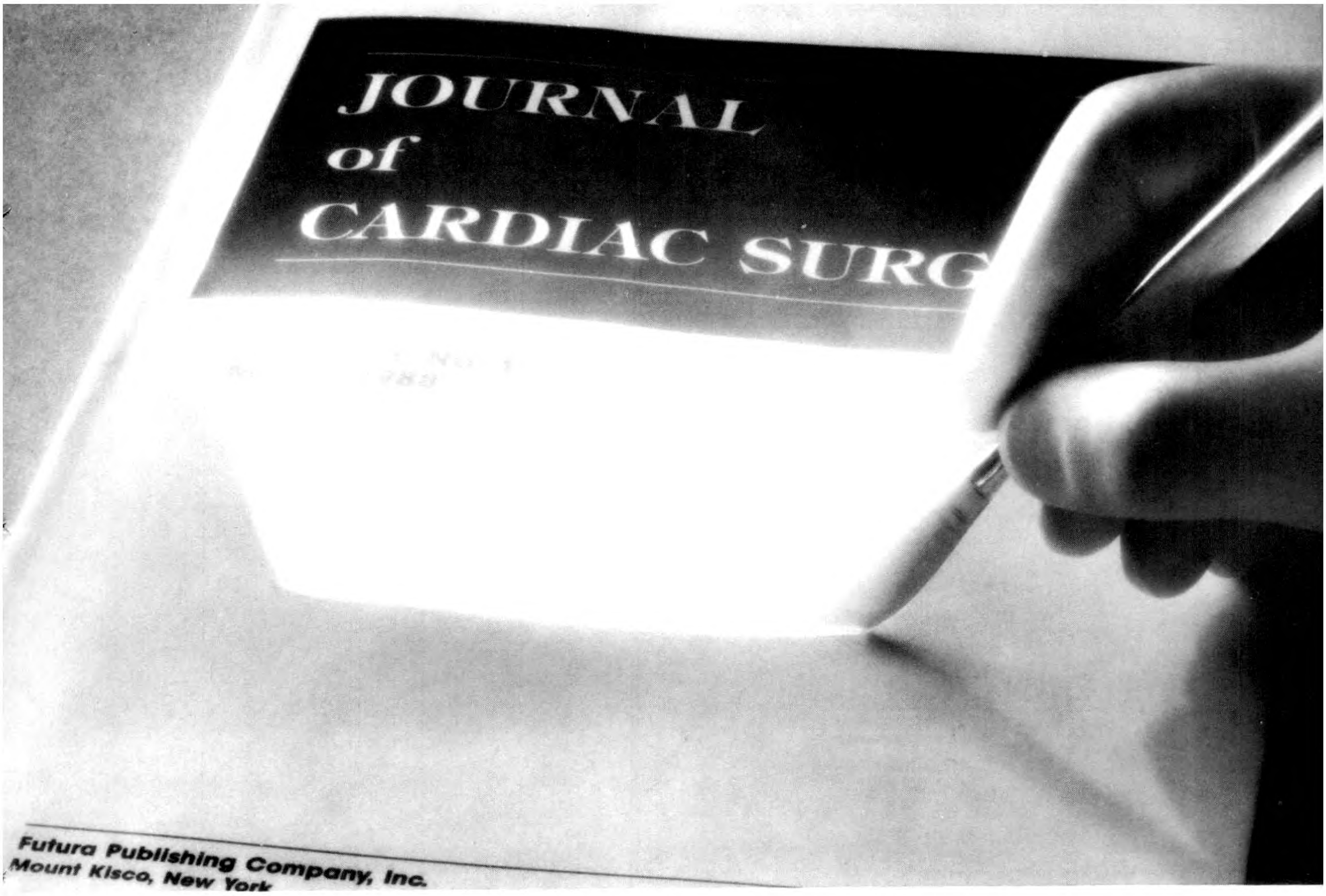

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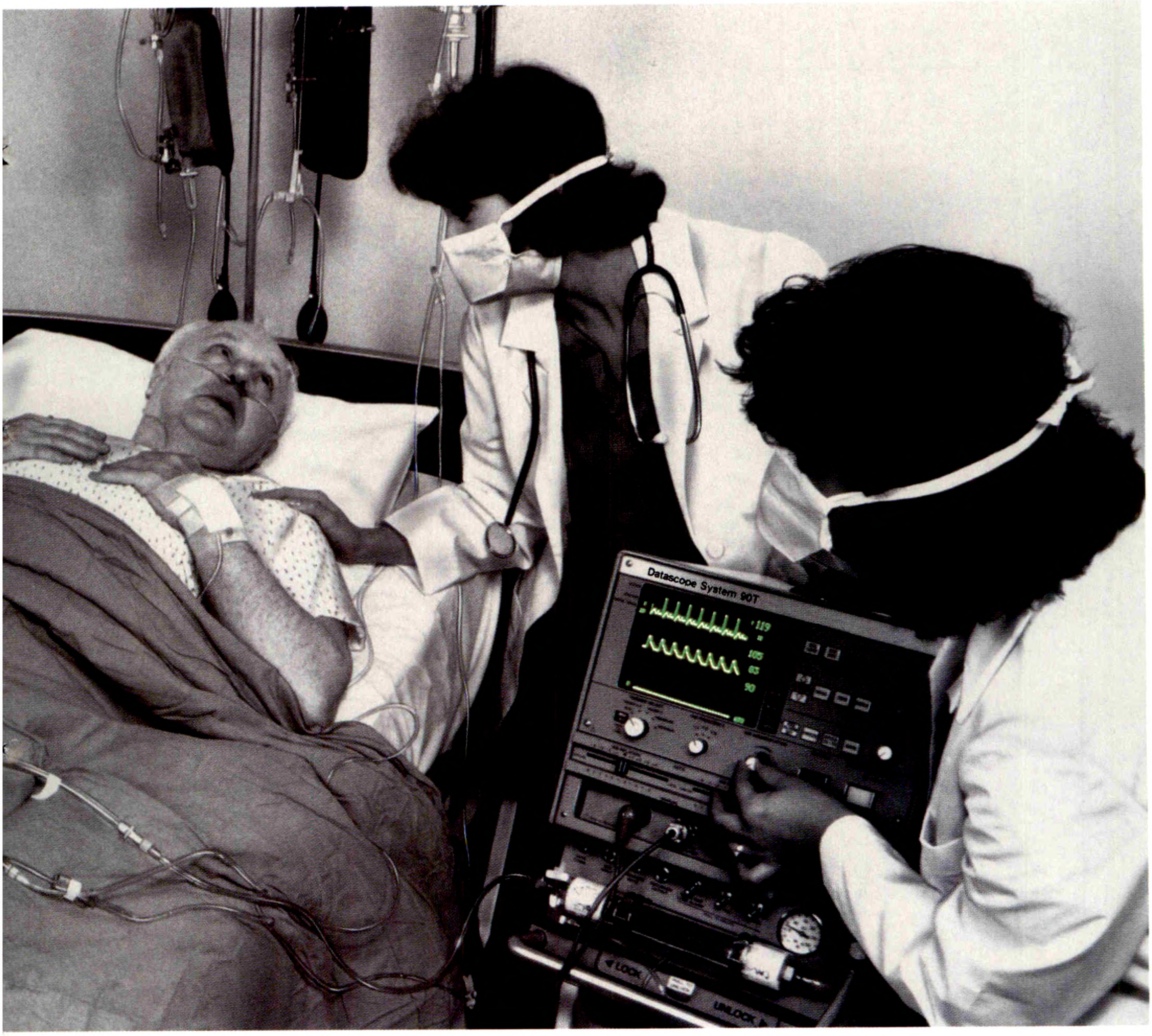

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CORONARY HEART DISEASE IN THE ELDERLY

Working Conference on the Recognition and Management of Coronary Heart Disease in the Elderly, held September 4-6, 1985, at the National Institutes of Health, in Bethesda, Maryland.

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Nanette K. Wenger, M.D., Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

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Elisabeth Pitt, M.A., Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Maryland

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Determinants of Homologous Blood Usage Utilizing Autologous Platelet-Rich Plasma in Cardiac Operations

Gerald F. Giordano, Sr, MD, Gerald F. Giordano, Jr, Shirley L. Rivers, MD, George K. T. Chung, MD, Robert B. Mammana, MD, Joseph D. Marco, MD, Allen R. Raczkowski, MD, Adib Sabbagh, MD, Richard G. Sanderson, MD, and Burt S. Strug, MD

Southern Arizona Regional Red Cross Blood Program; The Carondelet Health Care Network; El Dorado Hospital and Medical Center; and Tucson Medical Center, Tucson, Arizona

The present study evaluated (1) the influence of the collection of autologous platelet-rich plasma intraoperatively in addition to intraoperative autotransfusion on homologous blood usage and bleeding in cardiac operations; (2) the influence of age, sex, body surface area, type of operation, and reoperations on homologous blood usage and bleeding in cardiac operations utilizing intraoperative autotransfusion and autologous platelet-rich plasma collected intraoperatively; and (3) the influence of the preoperative administration of aspirin, Persantine (dipyridamole), heparin sodium, thrombolytic agents, Coumadin (crystalline warfarin sodium), and nonsteroid, antiinflammatory drugs on homologous blood usage and bleeding in cardiac operations utilizing intraoperative autotransfusion and autologous platelet-rich plasma collected intraoperatively. The results demonstrated a decrease in homologous blood use and bleeding when autologous platelet-rich plasma is collected in addition to the use of intraoperative autotransfusion. All of the patient and procedural variables influenced homologous blood usage and bleeding to some extent. Only the thrombolytic agents affected blood usage by increasing homologous plasma usage. All other drugs evaluated did not influence blood utilization or the amount of bleeding intraoperatively or postoperatively.

(Ann Thorac Surg 1989;47:897–902)

The realization that homologous blood is responsible for disease transmission, transfusion reactions, and autosensitization has led to increased interest in autologous blood products and blood conservation. Bleeding remains a major complication of cardiac procedures, and blood loss is a major concern for surgeons. Predeposit autologous programs offer the opportunity for patients to donate blood for themselves [1]. However, cardiac surgical patients frequently cannot take advantage of these programs because of the underlying disease and the often urgent nature of the cardiac operation. Intraoperative autotransfusion (IAT) has been demonstrated to decrease homologous blood usage in cardiac operation [2, 3], and a recent study [4] investigating selective versus constant IAT has demonstrated a significant reduction in homologous blood usage if IAT is used in all cardiac operations. Homologous plasma and platelet usage can be further reduced by the use of autologous platelet-rich plasma (PRP) collected in the intraoperative period [5].

Cosgrove and colleagues [6] evaluated the factors influencing blood usage in coronary revascularization procedures. Age, sex, weight, reoperation, and body surface area were determinants of homologous blood usage. Older patients received more homologous blood products, as did female patients, patients having reoperation, and patients with a smaller body surface area. A recent study [7] examined the effect of a low-dose (325 mg) preoperative ingestion of aspirin on postoperative blood loss. The aspirin-treated group differed significantly in the amount of postoperative bleeding (1,513 mL versus 916 mL), the number of units of red blood cells transfused (4.4 units versus 1.8 units), the amount of plasma transfused (3.6 units versus 1.6 units), and the number of platelet concentrates transfused (1.3 units versus 0.16 unit) [7]. This is in agreement with the findings of other authors [8, 9], who have demonstrated increased blood usage in surgical patients taking aspirin. Karwande and associates [10], however, were unable to find a relationship between preoperative aspirin ingestion and postoperative bleeding.

The present study was undertaken to (1) reevaluate the amount of homologous blood reduction when PRP was utilized along with IAT, with the inclusion of 398 additional patients to ascertain whether our initial observations remained valid [5]; (2) evaluate the effect of age, sex, body surface area, reoperation, percent plasma removed during operation, coronary artery bypass grafting (CABG) versus valve procedures, and cardiopulmonary bypass time on homologous blood usage when autologous PRP was used; and (3) evaluate the effect of the administration of aspirin and other anticoagulants on intraoperative and postoperative bleeding and homologous blood usage.

Accepted for publication Dec 30, 1988.

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Table 1. Sex of Patients and Types of Operation

	Type of Operation					
	CABG		Valve		Other[a]	
Sex	First	Redo	First	Redo	First	Redo
Male	216	36	28	3	2	0
Female	63	6	11	5	3	0
Total	279	42	39	8	5	0

[a] This means operation for congenital heart disease.

CABG = coronary artery bypass grafting.

Material and Methods

This study evaluated 373 consecutive cardiac surgical patients operated on in the years 1987 and 1988. Thirty additional patients were excluded because of death within the first 24 hours or unavailability of records. Patients who died in the first 24 hours were excluded because we thought their blood usage could not be adequately assessed. All patients received autologous PRP in addition to IAT as previously described [5]. In this program, autologous PRP is withdrawn from the patient at the time of operation and is reinfused to the patient after the effect of heparin sodium has been reversed by protamine sulfate [5].

Results in 147 patients undergoing consecutive operation in 1985 and 1986 with IAT alone were evaluated and compared with results in 373 patients receiving IAT plus PRP to further assess the influence of PRP plus IAT on homologous blood usage and bleeding with IAT alone. The blood use in 91 of these patients has been reported elsewhere [4].

Data Collection

Data concerning homologous blood usage and bleeding in cardiac operations were collected from hospital and blood center records, and blood usage was evaluated with reference to three categories of variables: the patient, the procedure, and the drugs used. All patients were included in the data analysis. In addition, the homologous blood usage of this group of patients was compared with that in a large series of patients in which IAT alone was used, as already detailed. Preliminary results have been previously reported [5], and this study extends those observations by including additional patients.

Patient and procedural variables were CABG or valve operation, age, sex, body surface area (computed by DuBois' formula), percent plasma removed (percent of estimated plasma volume removed as PRP product), cardiopulmonary bypass pump time, and reoperation or first operation.

Drugs examined were aspirin, Persantine (dipyridamole), nonsteroid, antiinflammatory agents, streptokinase or tissue plasminogen activator (TPA), preoperative heparin administration in therapeutic doses, and Coumadin (crystalline warfarin sodium). The time limits of drug administration prior to operation were: aspirin, seven days; Persantine, 48 hours; nonsteroid, antiinflammatory drugs, 48 hours; streptokinase or TPA, preoperative hospital stay; preoperative heparin, within 12 hours of operation; and Coumadin, seven days. We did not attempt to assess the homologous blood usage and bleeding as a function of the dose of these drugs.

Statistical Techniques

Analysis of results is divided into three sections: (1) the continued reduction in homologous blood usage when PRP was utilized in conjunction with IAT; (2) the effects of patient or procedural variables on blood use and intraoperative or postoperative bleeding in patients undergoing a cardiac operation with PRP and IAT; and (3) the effect of preoperative drug administration on total blood use and intraoperative or postoperative bleeding. Student's *t* test was used to evaluate the significance of reductions in blood component use, total blood use, and intraoperative or postoperative bleeding between the cohorts of patients—IAT alone and IAT plus PRP.

The second section of data analysis considered the effects of patient or procedural variables on blood usage and intraoperative and postoperative bleeding. Four separate multiple regression analyses were performed. Dependent variables were total homologous red blood cell usage, total homologous fresh frozen plasma usage, total homologous platelet usage, and total homologous blood use (total red blood cell, plasma, and platelet usage). Independent variables were age, sex, body surface area, valve or nonvalve procedure, cardiopulmonary bypass pump time, and reoperation.

The data were further evaluated by separating patients who underwent CABG procedures and those who underwent valve procedures. Multiple regression analyses were then performed as already described for both groups individually to assess whether the variables affecting bleeding are the same for patients undergoing CABG and patients undergoing valve replacement.

Independent of the multiple regression analyses, separate evaluations were performed to examine whether sex, type of operation (CABG or valve), and reoperation individually have a significant effect on blood use and intraoperative or postoperative bleeding. Two significance tests were performed for each variable: a standard *t* test and the Scheffé *F* test. The latter test was performed to

Table 2. Drug Use

Drug	No. of Patients[a]
Aspirin (CABG)	88 (27.4)
Persantine (CABG)	43 (13.4)
Streptokinase or TPA (CABG)	18 (5.6)
Coumadin (valve)	7 (14.9)
Heparin (all)	76 (20.4)
NSAID (all)	8 (2.1)

[a] Numbers in parentheses are percentages.

CABG = coronary artery bypass grafting; NSAID = nonsteroid, antiinflammatory drugs; TPA = tissue plasminogen activator.

Table 3. Difference in Homologous Blood Usage Between the Two Groups

Variable	PRP with IAT (n = 373)	IAT alone (n = 147)	Difference	p Value
Total blood use	5.31	12.91	7.60	0.0001
Total RBC (units)	2.34	3.44	1.10	0.0001
Total FFP (units)	1.02	3.32	2.30	0.0001
Total platelets (units)	1.94	6.15	4.21	0.0001
Total chest tube drainage (mL)	1,429.0	1,590.9	161.9	0.031
24-Hour chest tube drainage (mL)	1,088.5	1,193.4	104.9	0.056

FFP = fresh frozen plasma; IAT = intraoperative autotransfusion; PRP = platelet-rich plasma; RBC = red blood cells.

verify the results if the results of the t test were significant.

The third section of data analysis considered the effects of drug use variables on blood use and intraoperative or postoperative bleeding and homologous blood usage. Differences were evaluated for significance using Student's t test. Only CABG patients were considered in evaluating aspirin, Persantine, and streptokinase or TPA because clinically these patients are of greater interest and few candidates for valve procedures in the study had taken these drugs preoperatively. Similarly, only patients having a valve operation were considered in evaluating the effects of Coumadin, as it is most frequently employed under that condition. All patients are included in the evaluation of preoperative use of heparin and nonsteroid, antiinflammatory agents.

Results

The demographics of the patient population are demonstrated in Tables 1 and 2. Table 1 displays the case mix: CABG, valve, reoperation or first-time operation, and sex. Table 2 displays the percentage of patients taking the drugs that were evaluated. The average age in the series was 63 years (range, 15 to 81 years).

Repeat analysis of the difference in homologous blood usage utilizing PRP with IAT versus IAT alone is presented in Table 3. The differences between the PRP plus IAT group and the IAT group alone for total red blood cells, fresh frozen plasma, platelets, and total blood use were all significant at the 99% level. Total chest tube drainage was questionably significant at the 95% level, and 24-hour chest tube drainage was short of significance at the 95% confidence level. Homologous blood usage during operation has continued to decline since our initial observations concerning PRP were made [5]. Red blood cell usage has declined from 2.43 to 2.34 units per patient, plasma usage from 1.33 to 1.02 units per patient, and platelet usage from 2.56 to 1.94 units per patient.

The results of multiple regression analyses to assess the effects of patient or procedural variables are presented in Table 4. Significant indicators of homologous red blood cell use are age (with older patients requiring more blood), sex (with female patients requiring more blood), body surface area (with patients with a small body surface area requiring more blood), and pump time (with increasing blood use as pump time lengthens). Prolonged pump time and reoperation are significant predictors of homologous fresh frozen plasma use, and percent plasma removed approaches significance ($p = 0.0774$). Homologous platelet use is influenced by valve operation and cardiopulmonary bypass pump time, with valve operation requiring more platelet transfusions than CABG and increased pump times correlating with increased platelet use. Significant variables determining total homologous blood use are body surface area, pump time, and reoperation, although valve operation approaches significance at the 94% level.

The significance of these variables remained consistent when regression analyses were performed for valve and CABG patients separately.

Independent t-test results are presented in Table 5. Sex had a significant effect on homologous red blood cell use ($p = 0.001$), on both 24-hour and total chest tube drainage ($p = 0.0002$ and $p = 0.0009$, respectively), and on estimated intraoperative red blood cell recovery ($p = 0.0301$).

Table 4. Results of Multiple Regression Analyses to Assess Effects of Patient or Procedural Variables on Blood Usage[a]

Blood Usage	Age	Sex	Body Surface Area (m^2)	Valve Operation	Percent Plasma Removed	Pump Time	Redo
Homologous RBC	0.0122	0.011	0.0107	0.4224	0.5552	0.0001	0.4905
Homologous FFP	0.9819	0.6819	0.1394	0.2707	0.0774	0.0016	0.0004
Homologous platelets	0.6642	0.2194	0.155	0.0362	0.369	0.0001	0.1416
Total homologous blood use	0.3164	0.8668	0.0403	0.0611	0.2155	0.0001	0.0333

[a] All values are p values from multiple regression.

FFP = fresh frozen plasma; RBC = red blood cells.

Table 5. Results of Independent t *Tests*

Variable	Red Blood Cells (units)	Fresh Frozen Plasma (units)	Platelets (units)	Total Blood Use (units)	24-Hour Chest Tube Drainage (mL)	Total Chest Tube Drainage (mL)	Estimated IOS (mL)
Male	2.109	1.046	2.095	5.249	1157.4	1507.2	612.2
Female	3.08	0.955	1.455	5.489	865.6	1175.9	501.4
Difference	−0.971	0.091	0.640	−0.24	291.8	331.3	110.8
t Test *p* value	0.001	0.7399	0.3011	0.8104	0.0002	0.0009	0.0301
Scheffe's F test	11.078	. . .	. . .	. . .	14.573	11.116	4.743
(significance level)	(99%)				(99%)	(99%)	(96%)
First operation	2.263	0.848	1.734	4.845	1098.0	1427.9	553.7
Redo operation	2.82	2.16	3.3	8.28	1027.2	1436.1	795.0
Difference	−0.557	−1.312	−1.566	−3.435	70.8	−8.2	−241.3
t Test *p* value	0.1308	0.0001	0.0419	0.0055	0.4661	0.948	0.0001
Scheffe's *F* test	. . .	15.352	4.167	7.793	. . .	. . .	14.881
(significance level)		(99%)	(95%)	(99%)			(99%)
CABG	2.221	0.919	1.62	4.76	1093.6	1452.4	554.8
Valve	3.17	1.681	4.043	8.894	1032.8	1285.8	792.6
Difference	−0.949	−0.762	−2.423	−4.134	60.8	166.6	−237.8
t Test *p* value	0.0118	0.0284	0.0021	0.001	0.5321	0.1927	0.0002
Scheffe's F test	6.405	4.843	9.64	10.943	. . .	. . .	13.969
(significance level)	(98%)	(97%)	(99%)	(99%)			(99%)

CABG = coronary artery bypass grafting; IOS = intraoperative red blood cell recovery.

Reoperation had a significant effect on use of fresh frozen plasma, use of platelets, and total blood use (p = 0.0001, p = 0.0419, and p = 0.0055, respectively), and on estimated intraoperative red blood cell recovery (p = 0.0001). Type of operation (valve or CABG) was also a significant determinant of all blood use variables, that is, homologous red blood cells (p = 0.0118), fresh frozen plasma (p = 0.0284), platelets (p = 0.0021), and total blood use (p = 0.001), and of estimated intraoperative recovery of red blood cells (p = 0.0002).

Last, the effects of preoperative drug use on blood use and intraoperative or postoperative bleeding are presented in Table 6. As previously stated, only CABG patients are included in the evaluation of aspirin, Persantine, and streptokinase or TPA, and only valve patients are considered in evaluating Coumadin. All patients were considered in the evaluation of preoperative use of heparin and nonsteroid, antiinflammatory drugs. The only significant relationship concerning blood usage and bleeding is between thrombolytic drug agents (TPA or streptokinase) and homologous plasma usage (p = 0.0266). There was no relationship between the other drug agents studied and blood usage or bleeding.

Comment

The additional data collected support our earlier conclusion that autologous PRP decreases the usage of homologous blood products in cardiac operations [5]. The initial study did not demonstrate a significant difference in homologous red blood cell usage between IAT plus PRP and IAT alone. With additional patients in both the IAT and IAT plus PRP groups, the difference in red blood cell usage has attained significance at the 99% confidence level. The reduction in total postoperative bleeding is also now significant at the 95% level.

The continued decrease in homologous blood usage with IAT plus PRP and the fact that significance now exists with homologous red blood cell usage and postoperative bleeding as well as plasma and platelet usage further support the efficacy of the PRP product. In addition, this reduction in homologous blood usage has been achieved by multiple surgeons operating in multiple institutions in Tucson. The average red blood cell usage in the region at present (2.34 units per patient) is comparable to the recent data presented by Cosgrove [11] (1.8 units per patient on average). The changing characteristics of patients requiring a cardiac operation have increased blood usage [11], and this further supports the importance of decreasing blood usage by the use of IAT plus PRP.

Our data are similar to those of Cosgrove and associates [6], with age, sex, body surface area, and reoperation predictive of increased blood usage in a multiple regression analysis. This type of analysis produces the best assessment of the individual effects of the studied variables on blood usage, which is of special importance in evaluating the effects of sex and body surface area, two closely related variables. Pump time also influenced blood utilization, but the percentage of PRP removed did not affect blood transfusion, except for plasma; in that case, the amount removed correlated negatively with usage,

Table 6. Effects of Preoperative Drug Use

Drug	Red Blood Cells (units)	Fresh Frozen Plasma (units)	Platelets (units)	Total Blood Use (units)	24-Hour Chest Tube Drainage (mL)	Total Chest Tube Drainage (mL)	Estimated IOS (mL)
Aspirin (CABG)							
None	2.189	0.918	1.597	4.704	1,065.7	1,432.6	556.8
Within 7 days	2.307	0.92	1.682	4.909	1,167.4	1,504.9	549.7
t Test *p* value	0.6763	0.9940	0.8800	0.8202	0.1906	0.4853	0.8822
Persantine (CABG)							
None	2.201	0.885	1.604	4.691	1,087.6	1,448.6	548.0
Within 48 h	2.349	1.14	1.721	5.209	1,132.1	1,476.7	598.8
t Test *p* value	0.6905	0.4668	0.8747	0.6609	0.6622	0.8366	0.4141
Streptokinase/TPA (CABG)							
None	2.244	0.855	1.617	4.716	1,099.1	1,455.7	552.7
During hospital stay	1.833	2.0	1.667	5.5	1,000.6	1,397.2	590.3
t Test *p* value	0.4532	0.0266	0.9639	0.6543	0.5135	0.7712	0.6836
Coumadin (valve)							
None	3.275	1.725	4.0	9.0	1,076.9	1,328.3	768.8
Within 7 days	2.571	1.429	4.286	8.286	780.9	1,043.0	928.6
t Test *p* value	0.6022	0.7947	0.9279	0.8881	0.2615	0.3594	0.4966
Heparin (all)							
None	2.377	1.007	2.152	5.535	1,111.8	1,457.8	598.4
Within 12 h	2.184	1.092	1.132	4.408	997.5	1,316.6	537.8
t Test *p* value	0.5366	0.7678	0.1177	0.2836	0.1634	0.1840	0.2615
NSAID (all)							
None	2.337	1.027	1.953	5.318	1,096.4	1,437.6	587.3
Within 48 h	2.375	0.875	1.50	4.750	729.4	1,040.0	531.2
t Test *p* value	0.9651	0.8497	0.8028	0.8461	0.1076	0.1783	0.709

CABG = coronary artery bypass grafting; IOS = intraoperative red blood cell recovery; NSAID = nonsteroid, antiinflammatory drugs; TPA = tissue plasminogen activator.

that is, the more plasma removed, the less homologous plasma was used.

We postulate that the amount of autologous plasma and platelets removed in the PRP in this study was in excess of the amount needed to prevent clinical bleeding and that this explains the lack of correlation between the amount of PRP removed and clinical bleeding and blood transfusion. We attempted to withdraw 15% to 20% of estimated plasma volume (average percent removed, 18%) in our PRP product.

We used *t* tests to evaluate the effect of sex, reoperation, and type of operation on blood usage independent of the influence of other variables. We assessed their influence on chest tube drainage and intraoperative recovery of red blood cells as well as homologous blood utilization. Chest tube drainage and intraoperative recovery of red blood cells were not evaluated in the multiple regression analysis, as they would directly affect the amount of homologous blood utilized. Our data demonstrate that sex influences the amount of intraoperative and postoperative bleeding and red blood cell usage, but not plasma or platelet usage. Reoperations utilize more homologous blood products than initial operations and have a greater amount of intraoperative bleeding, but they do not have greater postoperative bleeding, perhaps as a result of the PRP product. A valve procedure also utilizes more homologous blood products and has increased intraoperative bleeding compared with CABG, but does not result in more postoperative bleeding than CABG.

Our study demonstrates the large percentage of patients with coronary artery disease who are taking antiplatelet agents, primarily aspirin and Persantine—27.4% and 13.4%, respectively. The most intriguing and controversial finding in the study was the lack of correlation between any of the drugs studied and blood usage or bleeding with the exception of streptokinase or TPA, which increased the transfusion of homologous plasma in CABG patients. The lack of correlation of aspirin, Persantine, or nonsteroid, antiinflammatory drugs with bleeding and homologous blood usage, amount of blood salvaged intraoperatively, and postoperative bleeding is perplexing in this group of patients in whom the autologous platelets circulating or collected as PRP would be expected to have an aggregation defect induced by these drugs. Furthermore, a survey of the cardiac surgeons involved in this study revealed that they uniformly believed that patients taking aspirin preoperatively bled substantially more than those not taking aspirin, a conviction not supported by the data. The amount of volume returned in the operating room as washed red blood cells was similar in both groups (see Table 6), which indicates that the patients who took aspirin did not have an excessive amount of intraoperative bleeding. The amount of blood salvaged during operation is not affected by the PRP product, as the latter is not returned until the patient is off cardiopulmonary bypass and heparin neutralization has been instituted.

We are not able to completely explain the lack of correlation between bleeding and antiplatelet drugs. The fact that the other determinants of bleeding, that is, age, sex, body surface area, and reoperation, were the same in our group of patients as in a group previously described [6] lends credibility to our data because it is difficult to postulate a variance of this magnitude occurring by chance when other observations are similar to those previously reported.

We did not evaluate the relationship of drug dose to bleeding and blood usage because we wanted to evaluate all patients and because the study was not large enough to divide patients by the amount of drug ingested and obtain meaningful data. These data will be obtained at a later time when the number of patients is larger and the results will be more meaningful.

Platelet release and aggregation is the result of the action of adenosine diphosphate, endoperoxidases, and thromboxane A_2 on platelets. Aspirin inhibits the production of endoperoxidases and subsequently thromboxane A_2 by blocking the enzyme cyclooxygenase [12]. However, thrombin can produce platelet aggregation by means of an alternative pathway. Circulating thrombin would be expected to be present during a cardiac operation as a result of the amount of tissue damage created, and this could explain the lack of an effect of aspirin on blood usage and bleeding.

In conclusion, we believe this study has confirmed our earlier observation that the intraoperative collection of PRP reduces homologous blood usage and bleeding in cardiac operations. The variables predictive of bleeding in cardiac surgery are the same when PRP is employed as when it is not. Our data also suggest that autologous PRP can be collected from all patients undergoing cardiac operations, as there was no relationship between the drugs evaluated and blood usage or bleeding with the exception of the effect of the thrombolytic agents on homologous plasma usage.

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Extracorporeal Membrane Oxygenation for Postcardiotomy Cardiogenic Shock in Children

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Size limitations and technical barriers prohibit the use of many conventional mechanical circulatory support systems for postcardiotomy ventricular dysfunction in pediatric populations. Extracorporeal membrane oxygenation (ECMO), frequently used to treat neonatal respiratory failure, can provide cardiac support and is effective treatment of postoperative myocardial failure in children. From 1981 to 1987, 10 patients aged 2 days to 5 years were maintained on ECMO for 15 to 144 hours (mean duration, 92 ± 16 hours) after cardiotomy. Operative procedures included repair of tetralogy of Fallot (2 patients), closure of a ventricular septal defect (2), the Senning procedure for transposition of the great arteries (1 patient), repair of interrupted aortic arch with closure of a ventricular septal defect (1), repair of a partial atrioventricular septal defect (2), closure of a ventricular septal defect with excision of an anomalous muscle bundle (1), and the Fontan procedure (1). Venoarterial ECMO was established in all 10 children. Six patients underwent transthoracic right atrium–ascending aorta cannulation, 3 had right internal jugular vein–right common carotid artery cannulation through a cervical incision, and 1 had right internal jugular vein–left axillary artery cannulation. Eight of the 10 patients were successfully weaned from ECMO, and 7 are long-term survivors. There were 3 deaths; 1 was caused by cardiac and acute renal failure complicated by sepsis two days after decannulation, another occurred 19 days after atrioventricular septal defect repair, and 1 was caused by massive pulmonary hemorrhage. Major hemorrhage developed in 3 patients while on ECMO; 2 required premature decannulation for mediastinal bleeding from operative sites and ultimately survived, and 1 died of respiratory failure as a result of endobronchial bleeding. We conclude that the use of ECMO in pediatric populations for transient postoperative ventricular dysfunction improves survival with limited overall morbidity.

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Mechanical circulatory support systems, intraaortic balloon counterpulsation, and ventricular assist devices for acute postcardiotomy ventricular failure effectively reduce postoperative mortality in adult populations [1]. Technological barriers, particularly size constraints, currently prohibit the clinical application of these devices to pediatric patients. Extracorporeal membrane oxygenation (ECMO), an effective method for treating respiratory distress in the newborn [2, 3], provides cardiac and pulmonary support and can be used to treat postcardiotomy ventricular dysfunction in infants and children [4–6].

This report details our clinical experience with 10 consecutive pediatric patients treated with ECMO for cardiac insufficiency after cardiopulmonary bypass. Findings from this study suggest that biventricular decompression achieved with postoperative venoarterial extracorporeal circulation permits satisfactory cardiac recovery with limited overall morbidity and mortality.

Material and Methods

During the 6-year period between 1981 and 1987, 10 children, 5 boys and 5 girls aged 2 days to 5 years, were treated with ECMO for severe postoperative right or biventricular failure refractory to maximal inotropic and vasodilator therapy. Weight of the patients ranged from 3.5 to 35 kg. Diagnoses and other patient data are shown in Table 1.

The general consensus among physicians involved in the care of these patients was that without mechanical circulatory support, mortality would exceed 90%. All 10 patients displayed signs and symptoms of inadequate cardiac output: systemic arterial hypotension, oliguria, poor peripheral perfusion, lactic acidemia, and diminished mixed venous oxygen saturation.

Venoarterial perfusion was used exclusively, with gravity drainage from the right atrium and return of arterialized flow to the aortic arch. The extracorporeal circuit currently used consists of a servoregulator, which automatically interrupts flow when venous return becomes inadequate, a heat exchanger to maintain normothermia, and a SciMed Kolobow spiral-coil membrane oxygenator for pulmonary support when required. Tygon polyvinyl chloride tubing, ¼ (0.625 cm) or ⅜ (0.9375 cm) inch in diameter, provided continuity between patient and circuit components. Flow rates ranged from 1.8 to 3.1 L/m^2 and averaged 2.41 L/m^2.

The time interval between operation and initiation of ECMO ranged from six to 54 hours in all patients except patient 4, who required ECMO immediately after bypass

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Table 1. Summary of Patient Data and Operative Data

Patient No.	Age	Sex	Weight (kg)	Diagnosis	Operative Procedure	Indications for ECMO
1	5 yr	M	15	Tetralogy of Fallot	Repair with transannular patch	Right ventricular failure
2	1 yr	M	8.4	Transposition of great arteries	Senning procedure	Biventricular failure
3	4 mo	F	3.9	AVSD (partial)	Repair with patch	Biventricular failure
4	5 yr	F	15	VSD and anomalous muscle bundle	Closure of VSD with patch and excision of anomalous muscle bundle	Biventricular failure
5	8 mo	M	7.2	VSD	Closure of VSD with patch	Right ventricular failure
6	2 mo	F	4.7	Tetralogy of Fallot	Repair with pulmonary valved conduit	Right ventricular failure
7	2 days	F	3.5	VSD, interrupted aortic arch (type A)	Closure of VSD and repair of interrupted aortic arch	Biventricular failure
8	3 mo	M	3.9	AVSD (partial)	Repair of ECP with patch	Biventricular failure
9	4 mo	F	3.5	VSD	Repair of VSD with patch	Biventricular failure
10	5 yr	M	35	Double-inlet left ventricle	Fontan procedure	Biventricular failure

AVSD = atrioventricular septal defect; ECMO = extracorporeal membrane oxygenation; VSD = ventricular septal defect.

for severe biventricular failure (Table 2). In patient 1, our first experience with ECMO for postoperative cardiogenic shock, an experimental 12-mL transfemoral intraaortic balloon counterpulsation device was introduced before ECMO decannulation; no other mechanical circulatory support systems were used in conjunction with ECMO in the remaining patients.

Six of the 10 patients had direct transthoracic right atrium–ascending aorta cannulation. Three patients underwent cervical cannulation: the venous cannula was introduced into the right atrium from the right internal jugular vein and the arterial cannula into the aortic arch from the proximal right common carotid artery with distal arterial ligation. Patient 1 underwent right internal jugular vein–left axillary artery cannulation. Continuous infusion of heparin sodium maintained whole blood activated clotting time between 180 and 240 seconds.

Inotropic therapy and ventilatory support was diminished or discontinued after the establishment of satisfactory ECMO flow. Cardiac recovery was determined by echocardiographic variables, which primarily included an overall assessment of contractility and cardiac function as measured by M-mode shortening fraction. These variables were clinically correlated with the hemodynamic consequences of diminished ECMO flow rates, with or without inotropic support.

Results

The salutary effects of improved hemodynamics were realized within hours of initiating ECMO. Systemic arterial blood pressure and urinary output increased, ventricular filling pressures declined, and lactic acidemia resolved. The duration of ECMO ranged from 15 to 144

Table 2. Extracorporeal Membrane Oxygenation Data and Complications

Patient No.	Weight (kg)	Interval Between Operation and ECMO (h)	Duration of ECMO (h)	Cannulation Site	ECMO Flow Rate (L/m^2)	Complications[a]	Outcome
1	15	46	48	Cervical	1.8	Renal failure, sepsis	Died
2	8.4	30	84	Cervical	2.26	None	Survived
3	3.9	24	134	Transthoracic	3.1	None	Died
4	15	. . .	48	Transthoracic	2.33	Pulmonary hemorrhage	Died
5	7.2	54	60	Transthoracic	2.44	Anoxic encephalopathy	Survived
6	4.7	72	96	Transthoracic	2.47	None	Survived
7	3.5	24	144	Cervical	2.43	None	Survived
8	3.9	7	160	Transthoracic	2.61	Mediastinal hemorrhage	Survived
9	3.5	6	15	Cervical	2.30	Mediastinal hemorrhage	Survived
10	35	24	96	Transthoracic	2.40	None	Survived

[a] Major complications developed in 5 of the 10 patients and were directly responsible for 2 of the 3 deaths. Patient 1 had renal failure necessitating peritoneal dialysis. *Escherichia coli* peritonitis developed, and he died. Endobronchial hemorrhage and severe aspiration pneumonia developed in patient 4 while she was on ECMO. She died of respiratory failure after cardiac transplantation.

ECMO = extracorporeal membrane oxygenation.

hours. Eight of the 10 patients displayed echocardiographic evidence of improved myocardial contractility within 48 hours after the initiation of ECMO. As ventricular function improved, ECMO was gradually tapered over a 24-hour period. Hemodynamic variables and the amount of inotropic support determined when decannulation could be safely performed.

Survival

Eight (80%) of the 10 patients were successfully weaned from ECMO, and 7 (70%) were long-term survivors. Two patients (20%) died shortly after ECMO was discontinued. In patient 1, acute right ventricular failure with subsequent renal failure developed after repair of tetralogy of Fallot. Support with ECMO was initiated 46 hours after operation. Peritoneal dialysis was started during ECMO and resulted in *Escherichia coli* peritonitis. Extracorporeal membrane oxygenation was discontinued because of the presence of severe septicemia, and the patient subsequently died as a result of cardiac and multiple-organ system failure. Autopsy revealed microabscess formation in the liver, lungs, and kidneys, and subsequent cardiac ventricular blood cultures were positive for *E coli, Pseudomonas*, and *Enterobacter*.

Patient 4, an infant with multiple congenital abnormalities born to a diabetic mother, failed to achieve satisfactory hemodynamics after closure of the ventricular septal defect and excision of an anomalous right ventricular muscle bundle; ECMO was initiated in the operating suite. Inferior wall myocardial infarction was suggested by the electrocardiogram and confirmed by echocardiography. Follow-up coronary arteriography, on ECMO, showed right coronary artery occlusion. After 24 hours of ECMO support, there was cessation of all cardiac activity. Cardiac transplantation was attempted on day 2 of ECMO, but postoperatively, massive hemoptysis resulted in respiratory failure. Chest roentgenograms revealed dense bilateral opacifications secondary to pulmonary hemorrhage; death due to respiratory failure ensued 18 hours after transplantation. Postmortem examination of the patient's native heart revealed large focal areas of ischemic necrosis; the cardiac allograft had a moderate amount of edema without cellular infiltrates.

Another patient, patient 3, was successfully weaned from ECMO but died during a subsequent cardiac procedure. This patient, a 4-month-old child with trisomy 21, had postoperative cardiac insufficiency after repair of a partial atrioventricular septal defect. After four days of ECMO support, decannulation was successfully accomplished. However, because of persistent respiratory failure and the echocardiographic finding of serious residual mitral regurgitation, cardiac catheterization was performed; it confirmed the presence of mitral insufficiency with pulmonary hypertension. Nineteen days later, the patient underwent mitral valve replacement. After cardiopulmonary bypass, severe left ventricular failure precluded restoration of satisfactory hemodynamics, and death occurred in the operating room. Permission for postmortem examination was not granted.

Complications

Major complications were infrequent in this series (see Table 2). Life-threatening hemorrhage developed in 3 patients while on ECMO. Two patients, patients 8 and 9, had mediastinal hemorrhage exceeding 30 mL/kg/h; therefore, decannulation and heparin reversal were required after 160 and 15 hours, respectively, of ECMO support. Sufficient ventricular recovery had occurred, and both children ultimately did well. Endobronchial bleeding in patient 4 produced a severe, diffuse aspiration pneumonitis, the primary cause of death after cardiac transplantation.

Five patients experienced at least one cardiopulmonary arrest before ECMO cannulation. Only 1 patient sustained neurological sequelae. Patient 5 underwent atrioventricular septal defect repair and had a cardiac arrest 24 hours postoperatively. Resuscitation, including ECMO cannulation, was performed with a satisfactory hemodynamic outcome; however, the transient cerebral anoxia led to a seizure disorder and temporary cortical blindness, which resolved 3 weeks later. The other survivors have completely recovered, and have normal physical and mental growth curves.

Comment

Early reports on the use of ECMO for respiratory failure also included a small number of adults and children with cardiogenic shock. The initial results, however, were generally poor, partly because ECMO support was chosen only for moribund patients after prolonged shock or periods of high-dose vasoconstrictor therapy. Pyle and associates [7] reported a series of 9 patients treated with ECMO; 2 had severe postcardiotomy ventricular dysfunction, and both died. Bartlett and co-workers [8] published a series of 28 patients, 4 of them children having operation for congenital heart defects; only 1 of the 4 children survived, a child with myocardial insufficiency after repair of tetralogy of Fallot. In 15 patients reported by Hill and colleagues [9], 6 underwent venovenous ECMO cannulation, 2 for ventricular failure, with no survivors. Four of the remaining 9 patients, maintained on venoarterial support, survived. Diagnoses included tetralogy of Fallot, cor pulmonale secondary to peripheral fat emboli, adult respiratory distress syndrome, and drug overdose.

The most promising results using ECMO support for postoperative myocardial dysfunction were obtained in pediatric populations. Redmond and associates [5] reported 4 (80%) of 5 pediatric patients survived with ECMO after surgical correction of congenital cardiac anomalies: 4 had total anomalous pulmonary venous connection and the other, coronary–ventricular fistula. The largest and most recent pediatric series of ECMO cardiac support [4] included 13 patients; the overall survival rate was 40%. A 70% survival rate reflects the experience with ECMO in our institution. In 1987, 44 newborns with respiratory failure were treated with ECMO with an 80% overall survival [3]. Our success may be attributable to the early aggressive use of ECMO before irreversible cellular events.

Two of the 3 patients who died postoperatively in our series had angiocardiographically documented structural abnormalities: patient 4 had a coronary artery injury, and patient 3 had persistent congenital mitral valve insufficiency. This finding indicates that ECMO is not successful when severe, irreversible myocardial damage is present or when major congenital abnormalities persist.

Although 1 patient died as a result of intrapulmonary hemorrhage soon after cardiac transplantation, the ability to provide prolonged cardiopulmonary support preserves cardiac transplantation as a viable option for patients with irreversible myocardial injury. Pennington and coworkers [10] reported 2 patients with acute and 1 with chronic cardiomyopathy who were initially treated with ECMO or a ventricular assist device. Those patients subsequently underwent cardiac transplantation, but with limited survival. In our institution, ECMO has also been used as a bridge to transplantation in a 15-year-old girl with severe end-stage cardiomyopathy disease (unpublished data).

Because of the necessity for complete anticoagulation, hemorrhage, particularly from operative sites, represents a serious potential complication during ECMO. Three of the 10 patients in this series required ECMO decannulation for substantial mediastinal bleeding. However, 2 of the patients were long-term survivors because sufficient cardiac recovery did occur on ECMO. Our 30% incidence of hemorrhagic complications compares favorably with that reported by Redmond [5] (25%), Kanter [4] (69%), Pennington [6] (85%), and their colleagues. Bleeding complications appear to be mitigated when the interval between the operative procedure and ECMO support exceeds six to eight hours, as patients 4, 8, and 9 with this complication began ECMO within this time interval.

Three patients were cannulated through the neck (right internal jugular vein and right common carotid artery). This approach avoids exposing the sternotomy incision to increased risks of mediastinal infections as previously reported [4]. In our experience, 6 of the 10 patients underwent mediastinal reexploration with transthoracic ECMO cannulation, and there were no mediastinal infections. Although no strict criteria were used to determine cannulation sites, the cervical approach was usually reserved for patients in the neonatal and early-infant stages, whereas the mediastinal approach was used in older patients. The mediastinal approach allows selection of optimal cannula size and position, and permits reassessment or revision of the operative repair.

The most prevalent complication preceding ECMO was renal azotemia due to acute tubular necrosis, the end result of inadequate renal blood flow. Six of the 10 patients displayed a greater than threefold increase in serum creatinine levels before ECMO. Five patients had nearly total resolution of renal dysfunction on ECMO, and 1 patient (patient 1) required dialysis. Currently, severe renal failure in neonates with respiratory insufficiency on ECMO is often treated by ultrafiltration or hemodialysis, as the extracorporeal circuit is easily adaptable to these interventions.

The relatively low overall incidence of major complications suggests that pediatric patients with severe postoperative cardiac insufficiency can be spared the consequences of prolonged shock and high-dose vasopressor therapy by early aggressive ECMO.

In evaluating myocardial recovery on ECMO, we found daily echocardiography very useful. Echocardiographic variables assessed overall contractility as well as cardiac function as measured by M-mode shortening fraction. Because there are many causes of reduced shortening fraction echocardiographically, the exact importance of a decreased shortening fraction is uncertain. Nevertheless, good contractility, as determined by shortening fraction irrespective of ECMO flow rates, was associated with successful weaning from ECMO. Current prospective studies are in progress to determine cardiac function in patients with presumably normal cardiac contractility while on ECMO for respiratory failure. More precise relationships between ECMO flow and overall contractility can then be determined.

In summary, postoperative ECMO cardiac support can effectively sustain patients who have undergone repair of a congenital heart condition by achieving right and left ventricular decompression while preserving peripheral organ system function. The overall complication rate in this series indicates that early ECMO for cardiogenic shock refractory to medical management can decrease long-term morbidity and mortality in the pediatric population.

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Myocardial Preservation Related to Magnesium Content of Hyperkalemic Cardioplegic Solutions at 8°C

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This study investigates whether the addition of magnesium to a hyperkalemic cardioplegic solution containing 0.1 mM ionized calcium improves myocardial preservation, and whether there is an optimal magnesium concentration in this solution. Isolated perfused rat hearts were arrested for two hours by this cardioplegic solution, which was fully oxygenated and infused at 8°C every 15 minutes to simulate clinical conditions. The cardioplegic solution contained either 0, 2, 4, 8, 16, or 32 mM magnesium. At end-arrest, the myocardial creatine phosphate concentration (nanomoles per milligram of dry weight) was 20.7 ± 2.1, 22.9 ± 1.7, 24.8 ± 2.0, 31.3 ± 1.4, 33.1 ± 1.8, and 31.6 ± 0.8, respectively, in hearts given cardioplegic solution containing these magnesium concentrations. Thus, the concentration of creatine phosphate was significantly higher at end-arrest when the cardioplegic solution contained 8, 16, or 32 mM than 0 or 2 mM magnesium ($p < 0.002$) or 4 mM magnesium ($p < 0.02$), and highest with 16 mM magnesium. Also, creatine phosphate was more sensitive to the magnesium concentration of the cardioplegic solution than was end-arrest adenosine triphosphate levels, which did not differ among the experimental groups. Aortic flow, expressed as a percentage of prearrest aortic flow, was 60.3 ± 5.0, 70.2 ± 5.5, 71.6 ± 4.4, 71.8 ± 4.8, 81.0 ± 5.0, and 71.8 ± 5.3, respectively. The addition of magnesium to the cardioplegic solution improved recovery of aortic flow ($p < 0.05$, 16 mM versus 0 mM magnesium). We conclude from these data that with deep myocardial hypothermia and at an ionized calcium concentration of 0.1 mM, the addition of magnesium, over a broad concentration range, improved preservation of myocardial creatine phosphate and, at a concentration of 16 mM, improved aortic flow. The optimal magnesium concentration in the cardioplegic solution was 16 mM.

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Magnesium in cardioplegic solutions can enhance myocardial preservation [1], and may act by antagonizing calcium or by maintaining transcellular magnesium levels during ischemia [2–5]. The present study investigates whether the addition of magnesium to a cardioplegic solution that contains 0.1 mM calcium would improve myocardial preservation and whether there is an optimal magnesium concentration in this cardioplegic solution.

Our cardioplegic solution contained an ionized calcium concentration of 0.1 mM, comparable with the ionized calcium concentration of the dilute blood cardioplegic solution used in our clinical practice [6]. Also, the cardioplegic solution was infused at 8°C to simulate our cardiac surgical conditions. Hearse and co-workers [2] showed in the isolated rat heart perfused at warmer temperatures with St. Thomas's Hospital solution, which has a substantially higher calcium concentration, that the addition of 15 mM magnesium gave the best functional recovery. This group [7] has stressed the need to determine the optimal concentration of each additive to a given cardioplegic solution. With deep hypothermia, which we employ, the optimal concentration of magnesium may be different from the concentration that provides the best preservation at warmer temperatures. Oxygenation [8] and multidose delivery [9] can further improve myocardial preservation with crystalloid cardioplegic solution, and represent additional factors not incorporated in the earlier study [2] that may alter the effect of magnesium.

For this study, we chose the isolated working rat heart model [7, 10] and assessed myocardial preservation from the end-arrest creatine phosphate (CrP) and adenine nucleotide concentrations and from the recovery of left ventricular function.

Material and Methods

Hearts were obtained from male Sprague-Dawley rats weighing 250 to 425 g. Animals were anesthetized intraperitoneally with sodium pentobarbital (65 mg/kg) and given 100 units of heparin sodium intravenously. The heart was excised and placed initially in iced Krebs-Henseleit bicarbonate buffer (Table 1). The heart was then mounted on the perfusion apparatus [7] and perfused initially for five minutes through the aortic root at a pressure of 100 cm H_2O by the method of Langendorff with the Krebs-Henseleit buffer, oxygenated with 95% oxygen and 5% carbon dioxide at 37°C in a reservoir above the heart. All solutions in this study were passed through a 5-μm-pore filter before administration.

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Table 1. Composition of Solutions

Variable		Krebs-Henseleit Bicarbonate Buffer	Base Cardioplegic Solution
Na^+	(mEq/L)	143.0	109.3
K^+	(mEq/L)	5.9	20.0
Ca^{2+}	(mEq/L)	2.4	. . .[a]
Mg^{2+}	(mEq/L)	2.4	. . .[b]
Cl^-	(mEq/L)	125.1	103.5
HCO_3^-	(mEq/L)	25.0	27.0
$H_2PO_4^-$	(mEq/L)	1.2	. . .
SO_4^{2-}	(mEq/L)	2.4	. . .
Glucose	(mM)	11.1	27.8
Mannitol	(mM)	. . .	54.9

[a] There was 0.1 mM ionized calcium. [b] To 1 liter of the base cardioplegic solution, 0 to 16 mL of a magnesium sulfate solution (2.03 mmol/mL) was added to give appropriate concentrations for the six groups, ie, 0, 2, 4, 8, 16, and 32 mM.

During the period of Langendorff perfusion, the left atrium was cannulated through a pulmonary vein. A working heart preparation was then established by perfusing the left atrium with the warm oxygenated Krebs-Henseleit buffer at a pressure of 16 cm H_2O and allowing the left ventricle to eject against a pressure of 95 cm H_2O into a recirculating aortic column [2, 7]. Aortic flow was measured by a flowmeter in the aortic column, previously calibrated by timed volumetric collection. Coronary flow was measured by timed volumetric collection of fluid draining from the heart. Heart rate was obtained from strip-chart recordings of the aortic pressure or the electrocardiographic tracings. Aortic flow, coronary flow, and heart rate were measured at five-minute intervals during the 20-minute prearrest stabilization period, the final measurements being taken as the prearrest control values. Hearts with an aortic flow less than 40 mL/min, coronary flow greater than 25 mL/min, or a heart rate less than 240 beats per minute, findings indicating possible damage during preparation, were rejected from the study.

At the end of the control period, the heart was rendered globally ischemic by clamping the left atrial and aortic catheters. Arrest was induced by the infusion of 15 mL of a cold, oxygenated, hyperkalemic crystalloid cardioplegic solution (see Table 1) at a constant pressure of 65 cm H_2O through a sidearm on the aortic cannula. The cardioplegic solution, in a water-jacketed reservoir supplying this sidearm, was continuously oxygenated at 4°C with 98% oxygen and 2% carbon dioxide. This resulted in an average pH of 7.41, an average carbon dioxide tension of 39.0 mm Hg, and an average oxygen tension greater than 800 mm Hg measured at 37°C in the cardioplegic solution, with 800 mm Hg being the upper limit of the measurement (Corning model 170 pH/blood gas analyzer; Ciba-Corning, Medfield, MA). After initial arrest, 10 mL of cardioplegic solution was infused by the same procedure every 15 minutes for a two-hour period. During arrest, the left ventricle was vented across the mitral valve by opening a fluid-filled catheter connected to the sidearm of the left atrial catheter to air, with the level of the open end adjusted so that no air entered the heart.

The heart was reperfused with Krebs-Henseleit buffer at 37°C in the Langendorff mode for 15 minutes. Coronary flow, temperature, and heart rate was recorded, and then the working mode was resumed for a further 30 minutes. Aortic flow, coronary flow, heart rate, and myocardial temperature were recorded at 5, 10, 15, and 30 minutes in the working mode.

The reservoirs and tubing of the perfusion apparatus and a chamber surrounding the heart were water jacketed for temperature control. Water at an appropriate temperature was supplied by pump circulators (Haake Buchler Instruments, Saddle Brook, NJ) with thermostats. Myocardial temperature, measured by a thermocouple probe placed in the right ventricle, was maintained close to 37°C during the control and reperfusion periods and at 8°C during arrest. Because function was often very temperature sensitive, care was taken to hold myocardial temperature during reperfusion as close as possible to the prearrest temperature, usually within 0.2°C.

Prior to administration of cardioplegic solution, at end-arrest, and at end-reperfusion, parallel groups of hearts were assayed for myocardial CrP and adenine nucleotides. Approximately 150 mg of ventricular apex tissue was excised and quickly frozen by compression between metal paddles precooled to −70°C. The frozen tissue was divided into three portions. Each portion was assayed for CrP, adenosine triphosphate (ATP), adenosine diphosphate, and adenosine monophosphate by high-pressure liquid chromatography as described previously [11, 12]. Heart water was determined by obtaining two samples from the ventricle remaining, desiccating them at 80°C, and averaging the results. The results of CrP and adenine nucleotide determinations were averaged and expressed as nanomoles per milligram of dry weight, using the heart water determined for each individual heart.

Experimental groups were differentiated by the magnesium content of the cardioplegic solution. Calcium and magnesium were added to the base cardioplegic solution in the following manner: Approximately 0.16 mL of a 10% solution of calcium chloride was added to a liter of the base cardioplegic solution, and the resulting ionized calcium concentration was determined (Nova 2 calcium ion selective electrode; Nova Biochemical, Newton, MA). The ionized calcium for all cardioplegic solutions was 0.104 ± 0.001 mM.

A volume of magnesium sulfate solution (2.03 mmol/mL) was then added to the cardioplegic solution as appropriate to the experimental group (see Table 1). No additional osmotic agent was added to compensate for the differences in cardioplegic solution osmolarity or in the dilution of other cardioplegic solution constituents (1.6% at most) among the experimental groups, as none would be added to the solution subsequently formulated for clinical use.

The sequence of experiments was determined by a blocked randomized design for pairs of hearts at a time. Groups differing by magnesium concentration in the cardioplegic solution were compared by one-way analysis of variance followed by *t* tests or Dunnett's test using

Table 2. Hemodynamic Variables[a]

Group (mM Mg^{2+})	n	Variable	Prearrest[b]	Reperfusion (min)[c]			
				5	10	15	30
0	8	Aortic flow (mL/min)	57 ± 3	34 ± 3	39 ± 3	41 ± 4	41 ± 4
		Coronary flow (mL/min)	19 ± 1	16 ± 2	16 ± 1	17 ± 1	17 ± 1
		Heart rate (beats per minute)	296 ± 13	298 ± 7	295 ± 8	301 ± 7	303 ± 12
		Cardiac output (mL/min)	75 ± 3	50 ± 3	56 ± 3	57 ± 3	58 ± 3
2	8	Aortic flow (mL/min)	61 ± 2	43 ± 4	46 ± 4	46 ± 4	43 ± 5
		Coronary flow (mL/min)	20 ± 1	16 ± 1	16 ± 1	17 ± 1	16 ± 1
		Heart rate (beats per minute)	314 ± 18	307 ± 18	302 ± 18	302 ± 17	294 ± 16
		Cardiac output (mL/min)	81 ± 2	59 ± 5	62 ± 4	63 ± 5	59 ± 6
4	8	Aortic flow (mL/min)	54 ± 3	39 ± 4	39 ± 3	39 ± 3	38 ± 4
		Coronary flow (mL/min)	19 ± 1	19 ± 2	19 ± 2	19 ± 2	20 ± 3
		Heart rate (beats per minute)	291 ± 13	283 ± 18	280 ± 15	281 ± 13	292 ± 14
		Cardiac output (mL/min)	73 ± 4	58 ± 5	57 ± 4	58 ± 4	58 ± 5
8	8	Aortic flow (mL/min)	61 ± 3	44 ± 3	45 ± 4	46 ± 3	46 ± 4
		Coronary flow (mL/min)	18 ± 1	17 ± 1	16 ± 1	16 ± 2	17 ± 2
		Heart rate (beats per minute)	309 ± 10	302 ± 11	298 ± 13	302 ± 11	294 ± 11
		Cardiac output (mL/min)	79 ± 4	61 ± 4	61 ± 5	62 ± 5	63 ± 6
16	8	Aortic flow (mL/min)	56 ± 2	46 ± 4	46 ± 2	47 ± 2	45 ± 1
		Coronary flow (mL/min)	21 ± 1	17 ± 1	17 ± 1	17 ± 1	17 ± 1
		Heart rate (beats per minute)	304 ± 10	300 ± 11	306 ± 10	303 ± 10	285 ± 11
		Cardiac output (mL/min)	77 ± 2	63 ± 4	63 ± 2	64 ± 2	62 ± 1
32	8	Aortic flow (mL/min)	59 ± 2	42 ± 3	43 ± 3	45 ± 2	43 ± 3
		Coronary flow (mL/min)	18 ± 1	17 ± 1	16 ± 2	17 ± 2	18 ± 3
		Heart rate (beats per minute)	304 ± 12	307 ± 10	306 ± 12	311 ± 10	288 ± 10
		Cardiac output (mL/min)	77 ± 3	59 ± 3	59 ± 2	62 ± 2	61 ± 2

[a] Data are shown as the mean ± the standard error of the mean. [b] Prearrest values were obtained at 20 minutes in the working mode. [c] The working mode was preceded by 15 minutes in the Langendorff mode.

BMDP statistical software program P7D [13]. Differences were considered significant at a p value of less than 0.05. Data are expressed as the mean ± the standard error of the mean.

All rats received humane care in compliance with the "Guiding Principles in the Care and Use of Animals" approved by the Council of the American Physiological Society (revised 1980) and the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985).

Results

Left Ventricular Function

Table 2 shows aortic flow, coronary flow, heart rate, and cardiac output recorded before arrest and during reperfusion. Figure 1 displays recovery of aortic flow expressed as a percentage of prearrest aortic flow. Percent recoveries were calculated for each individual animal to obtain the mean. Percent recovery of aortic flow at five minutes in the working mode in the 16 mM magnesium group (81% ± 5%) was significantly higher than in the 0 mM group (60% ± 5%) by Dunnett's test, although the tail probabil-

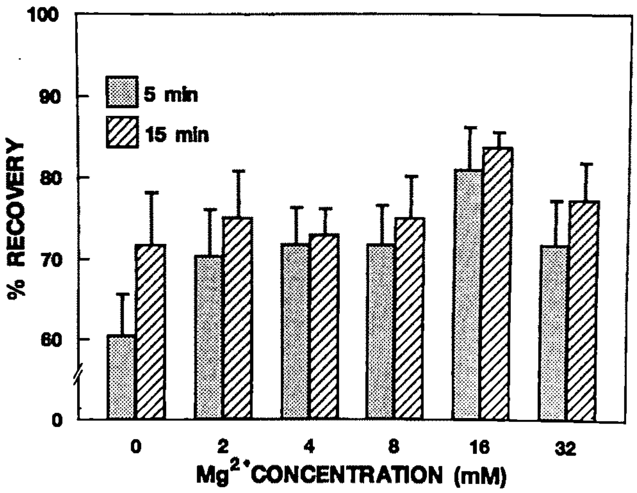

Fig 1. Recovery of aortic flow during reperfusion, expressed as a percentage of prearrest aortic flow for each individual animal, in the working mode (n = 8 in each group). Hearts were previously subjected to two hours of cardioplegic arrest and 15 minutes of reperfusion in the Langendorff mode. Error bars are ± the standard error of the mean.

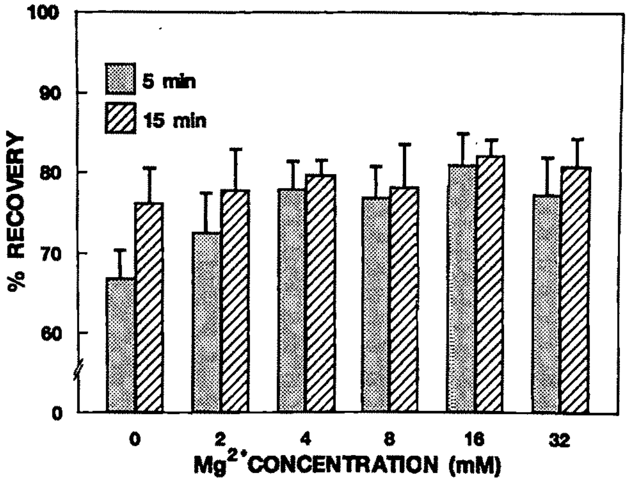

Fig 2. Recovery of cardiac output during reperfusion, expressed as a percentage of prearrest cardiac output for each individual animal, in the working mode (n = 8 in each group). Hearts were previously subjected to two hours of cardioplegic arrest and 15 minutes of reperfusion in the Langendorff mode. Error bars are ± the standard error of the mean.

ity of the *F* statistic was greater than 0.05. Although not significant, this difference persisted throughout the recovery period. There were no other significant differences among the groups for aortic flow.

Because coronary flow was a substantial portion of cardiac output, when it was added to aortic flow to calculate percent recovery of cardiac output at five minutes in the working mode, the difference in cardiac output between the 16 mM magnesium group and the 0 mM group was similar to the difference in aortic flow, but no longer significant (Fig 2). Again, there were no other significant differences among the groups for cardiac output.

Table 3. Myocardial Concentrations of Creatine Phosphate and Adenosine Triphosphate[a,b]

Group (mM Mg^{2+})	2-Hour Arrest			45-Minute Reperfusion[c]		
	n	CrP	ATP	n	CrP	ATP
0	9	20.7 ± 2.1[d]	10.1 ± 1.3	8	9.2 ± 0.9	6.1 ± 0.7
2	8	22.9 ± 1.7[d]	12.8 ± 1.6	8	10.0 ± 1.1	7.9 ± 0.9
4	9	24.8 ± 2.0[e]	10.2 ± 1.1	6	7.2 ± 0.9	6.1 ± 1.3
8	8	31.3 ± 1.4	10.3 ± 1.2	8	8.5 ± 1.0	5.1 ± 0.7
16	8	33.1 ± 1.8	9.6 ± 1.2	7	9.8 ± 1.0	6.5 ± 1.3
32	8	31.6 ± 0.8	11.1 ± 1.3	8	8.3 ± 0.8	5.2 ± 0.6

[a] Data are shown as the mean ± the standard error of the mean, and are measured in nanomoles per milligram of dry weight. [b] The prearrest values, measured in 8 hearts, were as follows: CrP = 8.6 ± 1.2; ATP = 9.3 ± 0.8. [c] This includes 15 minutes of reperfusion in the Langendorff mode followed by 30 minutes in the working mode. [d] At end-arrest, CrP levels in the 0 and 2 mM Mg^{2+} groups were significantly less than in the 8, 16, and 32 Mg^{2+} groups ($p < 0.002$). [e] At end-arrest, the CrP level in the 4 mM Mg^{2+} group was significantly less than in the 8 mM ($p < 0.02$), 16 mM ($p < 0.002$), and 32 mM ($p < 0.01$) Mg^{2+} groups.

ATP = adenosine triphosphate; CrP = creatine phosphate.

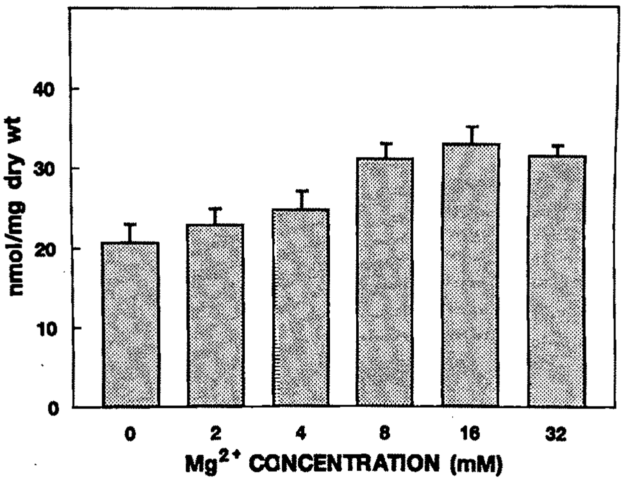

Fig 3. Myocardial creatine phosphate levels at the end of two hours of cardioplegic arrest (n = 8 or 9 in each group). Error bars are ± the standard error of the mean.

High-Energy Phosphates

Table 3 shows myocardial concentrations of CrP and ATP. The CrP concentration was highest at end-arrest in the 16 mM magnesium group (Fig 3). The CrP levels were paralleled by the recovery of aortic flow and cardiac output in the working mode. After two hours of arrest, the CrP concentration was higher in all groups than in the prearrest control group. After reperfusion, CrP returned to values close to the prearrest value. Levels of ATP, adenosine diphosphate, and adenosine monophosphate showed no significant differences among the groups at end-arrest or end-reperfusion. All solutions preserved ATP at or above the prearrest concentration for the two-hour arrest period, but ATP levels decreased somewhat during reperfusion.

Heart Water

Table 4 shows percent heart water at prearrest, end-arrest, and end-reperfusion. At end-arrest, there was

Table 4. Heart Water[a,b]

Group (mM Mg^{2+})	2-Hour Arrest		45-Minute Reperfusion[c]	
	n	Heart Water (%)	n	Heart Water (%)
0	9	81.8 ± 0.2[d]	8	83.5 ± 0.3
2	8	81.5 ± 0.2[d]	8	83.0 ± 0.3
4	9	82.1 ± 0.4[e]	6	83.1 ± 0.2
8	8	83.3 ± 0.4	8	83.0 ± 0.4
16	8	83.3 ± 0.2	7	84.0 ± 0.5
32	8	83.7 ± 0.2	8	83.6 ± 0.2

[a] Data are shown as the mean ± the standard error of the mean. [b] The prearrest value, measured in 8 hearts, was 82.4% ± 0.3%. [c] This includes 15 minutes of reperfusion in the Langendorff mode followed by 30 minutes in the working mode. [d] At end-arrest, percent heart water in the 0 and 2 mM Mg^{2+} groups was significantly less than in the 8, 16, and 32 mM Mg^{2+} groups ($p < 0.0004$). [e] At end-arrest, percent heart water in the 4 mM Mg^{2+} groups was significantly less than in the 8, 16, and 32 mM Mg^{2+} groups ($p < 0.004$).

significantly higher percent heart water with increasing magnesium levels in the cardioplegic solution. Heart water generally increased during reperfusion, but there were no significant differences among the groups by the end of reperfusion.

Comment

The purpose of the study was to find the optimal magnesium concentration for myocardial preservation in a cardioplegic solution containing 0.1 mM ionized calcium when the solution was used to produce hypothermic arrest at 8°C. We found that the CrP level at end-arrest in hearts protected by the cardioplegic solution containing 16 mM magnesium was higher than with any other magnesium concentration, some 50% higher than in the absence of magnesium and significantly higher than CrP in hearts protected by the cardioplegic solution with 4 mM magnesium or less. Although significance was borderline, a concentration of 16 mM magnesium also provided the best percent recovery of aortic flow and cardiac output during early reperfusion, and maintained the highest recovery of both these variables throughout the entire reperfusion period.

Intracellular magnesium exists largely as a complex with adenine nucleotides and has a concentration of 17.3 ± 0.3 mmol/kg cell water in rat myocardium [14]. The cytosolic concentration of the free magnesium ion is much lower, nearer 1 mM, which is similar to the extracellular magnesium concentration of 0.5 to 1.5 mM [15]. The exchange of magnesium between intracellular and extracellular compartments is slow, with a half-time in the rat ventricle of approximately three hours [16]. A loss of magnesium during ischemia may restrict cellular function and the resumption of normal metabolic and contractile function. Magnesium in cardioplegic solutions may provide tissue preservation by preventing ischemic cellular loss of magnesium and also may combat some deleterious consequences of potassium arrest, particularly those related to increased calcium influx [3, 4].

Magnesium has interactions with calcium, and its beneficial effects as a cardioplegic additive may be dependent on antagonism of calcium by magnesium [2, 4]. Magnesium antagonizes the effects of calcium at the sarcolemma and mitochondria, and reduces calcium influx during ischemia. As shown by Boggs and associates [17] in the rat heart, a hyperkalemic cardioplegic solution that was acalcemic proved superior to the same solution with the addition of even a small amount of calcium (0.25 mM ionized calcium). The addition of calcium to cardioplegic solution may decrease myocardial preservation in part by inducing tension development during arrest and thereby increasing energy consumption [2, 18].

Increases in left ventricular diastolic pressure during cardioplegia infusions have been observed recently in our laboratory in the isolated isovolumic rat heart and are associated with decreased myocardial high-energy phosphates [19]. When energy production was limited by hypoxia or by the absence of substrate, repeated infusions of cardioplegic solution containing calcium resulted in contracture. As contracture is a state of energy depletion, these observations suggest that the cardioplegic solution infusions and associated pressure development deplete myocardial energy reserves [19]. Diastolic pressure during cardioplegia infusion was greatly diminished by the addition of magnesium to the calcium-containing cardioplegic solution [19].

We [20] recently confirmed that the addition of 0.1 or 1.2 mM calcium to a cardioplegic solution increases the magnitude of diastolic pressure development during infusion of the cardioplegic solution in a dose-dependent manner. At either of these calcium concentrations, end-arrest myocardial high-energy phosphates were depleted and functional recovery was diminished. The addition of 16 mM magnesium to either of these calcium-containing solutions diminished the pressure development during cardioplegia, prevented high-energy phosphate depletion, and enhanced subsequent recovery of left ventricular developed pressure [20].

This previous study [20] and the present study differ in certain respects. In the previous study but not the present study, the left ventricle contained an isovolumic balloon to investigate diastolic tone, which was recorded as pressure development, during arrest; probably in part as a result of this pressure development, the cardioplegic solution containing 0.1 mM calcium but no magnesium caused end-arrest ATP depletion. The same solution did not cause ATP depletion in the present study, in which the ventricle could empty across the mitral valve during arrest and so, presumably, developed little or no pressure; instead it manifested contractile activity as shortening with less energy consumption. In this respect and also in the use of the ejecting rather than isovolumic model before arrest and during reperfusion, the present study is closer to the clinical situation. However, the isolated perfused heart is not stable for a sufficient period for study of long-term effects of cardioplegia.

Pernot and colleagues [18] evaluated the substitution of magnesium for hyperkalemia in a cardioplegic solution containing 0.25 mM calcium, and found that this substitution increased end-arrest myocardial CrP concentrations and significantly improved early recovery of ventricular function. In general accord with those researchers, our present study showed that the addition of magnesium to a hyperkalemic calcium-containing cardioplegic solution increased CrP concentrations at end-arrest and increased recovery of ventricular function during reperfusion. These beneficial effects are probably due to an antagonism between magnesium and calcium.

Hearse and co-workers [2] demonstrated enhanced myocardial preservation with a cardioplegic solution containing magnesium at temperatures of 28° and 37°C. They found that the optimal magnesium concentration was 15 mM in St. Thomas's Hospital cardioplegic solution, which has a calcium concentration of 1.2 mM and a potassium concentration of 16 mM. In our study, although differences in functional recovery among the groups were small, the optimal concentration of magnesium was 16 mM for maximal end-arrest CrP levels. However, the end-arrest CrP level was not significantly different when the cardioplegic solution contained 8 or 32 mM magnesium. Experimental conditions and cardioplegic solution formulations differ between our study and the St. Thomas's Hospital study, but in both studies, the optimal magnesium concentrations were similar despite an approximately tenfold difference in calcium concentrations. There was, therefore, no correlation between the optimal magnesium concentration and the calcium concentration.

In our study, the CrP concentration at end-arrest was substantially increased above its prearrest value in all groups, but more so at the higher cardioplegic solution magnesium concentrations, thus indicating that CrP production exceeded consumption in the cold arrested hearts. A high myocardial content of CrP at end-arrest appears to correlate with enhanced functional recovery during reperfusion in this study. At the end of reperfusion, CrP had returned to prearrest levels in all groups. End-arrest ATP was at or higher than the prearrest level in all groups. Although these data provide no information on high-energy phosphate compound flux or distribution between subcellular compartments, they suggest good preservation of these compounds. However, the reason for the uniform decline in ATP levels during reperfusion, and whether this decline reflects some failure of protection during arrest or reflects injury during reperfusion, is unknown.

The measurement of heart water does not distinguish between water in intracellular, interstitial, and intravascular tissue compartments. Heart water at end-arrest was higher in hearts given cardioplegic solutions with 8 mM magnesium or more. This may relate to the lower resting tone during arrest induced by magnesium in the cardioplegic solution [20]. Increased heart water was not related to impaired functional recovery during reperfusion, however, as functional recovery was best at a magnesium concentration of 16 mM. By end-reperfusion, there were no differences in heart water among the groups.

All groups of hearts in this study were well protected by deep hypothermia and a multidose oxygenated hyperkalemic cardioplegic solution. In all groups, cardiac output recovered to 75% or more of its prearrest value by 15 minutes of reperfusion. Although it is difficult to establish differences between groups of hearts that were all well protected, the observations in this study together with previous observations by us [19, 20] and others [2, 4, 18] provide a rationale for including magnesium in calcium-containing hyperkalemic cardioplegic solutions. The present data suggest that 16 mM is in the optimal concentration range for magnesium in our solution.

In conclusion, we showed that hearts preserved by a hyperkalemic cardioplegic solution containing a small amount of calcium without the addition of magnesium had the lowest CrP concentrations at end-arrest and poorest percent recovery of aortic flow and cardiac output throughout the reperfusion period. When magnesium was included in this cardioplegic solution, CrP levels at end-arrest increased substantially and ventricular recovery improved modestly. Both of these variables were optimal at a concentration of 16 mM magnesium. These observations support the use of 16 mM magnesium in our cardioplegic solution.

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REVIEW OF RECENT BOOKS

Intravascular and Intracardiac Interventional Catheter Therapy. Techniques and Instrumentation
Edited by T. Bonzel and P. W. Serruys
Vienna, Springer-Verlag, 1987
123 pp, illustrated, $35.50

Reviewed by Timothy J. Gardner, MD

Developments in the field of interventional catheter therapy, a field that includes coronary and peripheral vascular angioplasty, cardiac valvuloplasty, and coronary thrombolytic interventions, have obvious implications for cardiovascular surgeons. Clinical experience with such techniques, in particular with coronary angioplasty, has grown at an exponential rate over the last several years, as improved instrumentation and technical refinements have fostered an increasingly bold and aggressive approach in the catheterization laboratories. The book under review, which is actually a special supplement of the *Zeitschrift fur Kardiologie*, the German journal of cardiology, includes papers presented at a symposium held in 1987 for the intended purpose of defining the state of the art of interventional catheter therapy. Many papers in the volume report on experiences at European centers, although the extensive coronary angioplasty experience at Emory is reviewed by Spencer B. King, and there is also an excellent review of the role of platelet–endothelial wall interactions and antithrombotic therapy for coronary angioplasty presented by Munson and Fuster from the Mt. Sinai School of Medicine in New York.

Although the individual papers in this volume vary considerably in importance or relevance for a current understanding of interventional catheter therapy, the time devoted to a review of this material will provide the reader with a moderately useful background. Dr King's review of the Emory University Hospital experience with 7,000 coronary angioplasty procedures performed between 1980 and 1987 is helpful in providing what must be a "best case" report of coronary angioplasty. What is not included in Dr King's report is information about the role of angioplasty in multivessel coronary disease, data that, in fact, may not have been available in 1987 but are clearly of particular interest to those of us who must deal today with the complications of high-risk angioplasty procedures. The papers describing the use of percutaneous aortic and mitral valve dilations are similarly limited, in that the reports have a preliminary character to them. Although these techniques should be considered for the management of some patients with valvular stenoses, the reports in this volume, which were prepared in 1987, do not include information that is really needed today; ie, for whom should these procedures be reserved, and how many of these patients remain improved by catheter treatment at 6, 12, or 24 months later? Other papers in the volume describe specific technical innovations and developments and are of some usefulness to the reader as background information.

What is missing from the volume is an editorial perspective, which would be helpful in providing the noncardiologist or nonradiologist with an overview with which to evaluate the importance and relevance of the various reports. If discussions of the various papers, which presumably occurred at the symposium, were included with the papers, the reader would, perhaps, be better informed. The absence of this type of editorial or "peer" review and the additional limitation that reports generated in this rapidly developing field 2 years ago may no longer be relevant to current practice reduce the potential usefulness of this volume for cardiac surgeons, despite our substantial interest in the field of catheter therapy.

Baltimore, MD

Detection of Cold Hemagglutination in a Blood Cardioplegia Unit Before Systemic Cooling of a Patient With Unsuspected Cold Agglutinin Disease

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A case is described in which hemagglutination occurred intraoperatively in cold blood flushed through the blood cardioplegia delivery system from a patient with unsuspected cold agglutinin disease. On initiating cardiopulmonary bypass and then selectively cooling the perfusate in the blood cardioplegia delivery system before inducing systemic cooling, it is possible to check for cold agglutination. Routine use of this technique may be worthwhile to detect cold agglutination in vitro before systemic cooling is begun in the rare patient with unsuspected cold agglutinins.

(*Ann Thorac Surg 1989;47:914–5*)

Hypothermic cardiopulmonary bypass carries the risk—however remote—of red cell agglutination caused by unsuspected cold agglutinin disease. Today's efficient blood cardioplegia systems that deliver sanguinous solutions at 5° to 10°C may precipitate cold agglutination in the rare patient with this disease.

If cold agglutinin disease is recognized before operation, alternatives such as preoperative plasma exchange [1] or use of warm crystalloid cardioplegia to displace the blood in the heart before cardioplegic cooling [2, 3] are available. Alternatively, operation may be conducted at normothermia.

These methods assume the problem is recognized before cooling is begun. However, pretransfusion testing is not designed to identify cold agglutinins, particularly those of low thermal amplitude. As cold agglutinin disease is frequently asymptomatic, patients could come to operation with unsuspected disease. Obviously it is desirable to recognize the problem before agglutination occurs in vivo.

A case is described in which hemagglutination was observed intraoperatively, but before systemic cooling, in cold blood flushed from the cold blood cardioplegia unit. This discovery allowed avoidance of systemic hypothermia and cold blood cardioplegia.

A 65-year-old man with triple-vessel coronary artery disease and a 16-mm Hg peak systolic gradient across his aortic valve was scheduled for coronary artery bypass grafting and aortic valve decalcification. The left ventricle was moderately hypokinetic.

Pretransfusion testing microscopically identified a cold alloantibody with M specificity; a positive direct antiglobulin test due to complement only and no spontaneous agglutination. The specimen was tested directly with no refrigerator storage. Compatible units of blood were obtained and operation was planned using systemic hypothermia to 25°C with cold blood potassium cardioplegia infusion at 5° to 10°C.

Cannulas were inserted and cardiopulmonary bypass instituted at 37°C. With the patient at normothermia, the cardioplegia unit (Electromedics D720 cardioplegic heat exchanger with 4:1 blood/crystalloid dilution tubing) was cooled with ice water from the heater-cooler (our normal procedure). The prime was flushed out and displaced with blood from the bypass circuit, and the effluent was collected. Distinct separation of red cells from the crystalloid-plasma mixture was noted. Cold agglutinin disease was suspected. Examination revealed red cell agglutination that reversed completely after warming to 37°C.

To prevent potential harm to the microcirculation, bypass was maintained at normothermia and no cardioplegia was used. The heart was perfused and fibrillation induced electrically with subsequent discontinuation of the current. One left internal mammary artery graft and three distal reverse saphenous vein grafts were performed. A ten-minute cross-clamp period was used during one of four distal grafts. The other distal anastomoses were accomplished with local coronary occlusion. Because of the inability to cool the patient, the aortic valve was not inspected. This could complicate the procedure and expose the patient to the substantial risk of normothermic ischemia to decalcify a valve with a minimal gradient. After 91 minutes of fibrillation, the heart was defibrillated once at 10 J and allowed to beat while the two proximal anastomoses were made. The patient was weaned from bypass after a total of two hours 16 minutes.

Subsequent patient evaluation revealed no viral infection, malignancy, or autoimmune disorder. A cold agglutinin titer of 1:2,048 at 1° to 5°C (Fig 1) and a microscopically positive direct antiglobulin test due to complement only are consistent with idiopathic cold agglutinins. The

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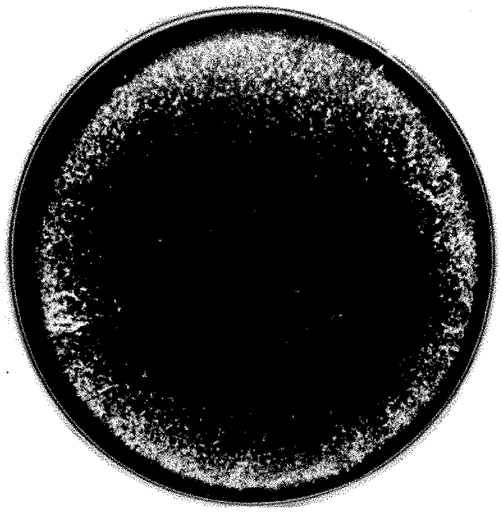

Fig 1. Cold hemagglutination of patient's whole blood in vitro.

postoperative course was free of cardiac complications. Serial tests of the MB isoenzymes of creatine kinase did not reveal perioperative myocardial infarction (peak value, 26 IU/L) and serial electrocardiograms had no new Q-wave.

Comment

Cold agglutinin disease, an autoimmune phenomenon in which antibody directly agglutinates red cells at temperatures below body temperature and maximally at 0° to 5°C, is most frequently asymptomatic but may cause hemolytic anemia or peripheral vessel occlusive phenomenon, usually initiated by cold exposure. The disease may be associated with infection or with lymphoproliferative or autoimmune disorders [4]. The idiopathic form has a peak incidence after age 50 years, a usual age for cardiac bypass procedures.

Thermal amplitude of cold agglutinins, the highest temperature at which agglutination occurs, is rarely more than 30°C and usually less than 25°C, particularly in the asymptomatic patient. Pretransfusion testing performed on freshly obtained specimens occurs at room temperature at the lowest and can miss agglutination when the thermal amplitude is less than room temperature. Therefore, cold agglutinins of low thermal amplitude can be missed in pretransfusion testing using recently drawn specimens with no refrigerator storage. On the other hand, many "cold" reacting antibodies observed at room temperature during routine pretransfusion testing do not cause direct spontaneous agglutination or hemolysis of red cells in vivo and are routinely considered not to be clinically significant even in patients undergoing hypothermia. Because cold agglutinin disease is rare, testing for this phenomenon is not usually done.

It is clear that our technique allowed us to recognize agglutination in the cardioplegia unit and prevent possible massive agglutination. Once discovered, the problem was circumvented by a normothermic method of myocardial protection.

We believe this technique of cooling the cardioplegia unit alone first will help detect cold agglutinins in vitro before systemic cooling in the rare patient with unsuspected cold agglutinin disease.

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Successful Repair of Left Ventricular Rupture After Redo Mitral Valve Replacement

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A patient with an extensive type I left ventricular rupture after a redo mitral valve replacement was successfully treated using a patch of glutaraldehyde-preserved pericardium sutured to the endocardium around the tear.

(Ann Thorac Surg 1989;47:916–7)

Rupture of the posterior wall of the left ventricle after mitral valve replacement is usually lethal [1–8]. Even when recognized early intraoperatively, attempts at repair using externally applied sutures usually result in failure. A patient with this complication was successfully treated with a pericardial patch sutured to the endocardium around the tear. This technique permits accurate repair of even extensive disruptions of the left ventricle.

A 57-year-old man who had received a No. 31 porcine mitral valve replacement 10 years earlier was seen with progressive shortness of breath on exertion and a murmur of mitral insufficiency. Cardiac catheterization confirmed substantial mitral valve insufficiency. The patient underwent replacement of the porcine mitral valve prosthesis. The old prosthesis was removed, care being taken not to excise tissue surrounding the old valve ring. A No. 31 Carpentier-Edwards bioprosthesis was used as a replacement.

During initial weaning from cardiopulmonary bypass, major bleeding was noted from the area of the posterior atrioventricular groove. Total cardiopulmonary bypass was immediately reinstituted. The patient was again cooled, the aorta was cross-clamped, and the heart was rearrested using cold blood cardioplegia. The left atrium was reopened and the bioprosthesis was removed. A complete discontinuity between the atrium and the ventricle was noted. Only the region of the mitral valve annulus between the left and right fibrous trigones was spared.

To repair this disruption, an elliptical piece of glutaraldehyde-preserved bovine pericardium was sutured to the endocardium 1 to 2 cm from the borders of the tear using a running 4-0 polyproplene suture. The bioprosthesis was then replaced and secured to the atrial surface of the patch using pledget-supported sutures. An intraaortic balloon pump was inserted and the patient was taken off cardiopulmonary bypass with inotropic support.

The intraaortic balloon pump was removed on the first postoperative day. Postoperative hypertension was carefully prevented. There were no cardiac enzyme or electrocardiographic changes suggesting intraoperative myocardial infarction. The patient subsequently made an uneventful recovery and was discharged from the hospital.

Comment

Rupture of the posterior wall of the left ventricle after mitral valve replacement is an unusual complication with an incidence of 0.5% to 7.5% [2, 3, 5]. It is usually lethal unless it is recognized intraoperatively [1, 4, 5, 7–9]. Rupture of the ventricle is classified according to the site of rupture. In type I the tear occurs in the mitral annulus or just below it along the atrioventricular groove; in type II the ventricular rupture originates at the site of the base of an excised papillary muscle; and type III or midventricular rupture is located between the atrioventricular groove and the papillary muscles [6, 7].

Etiological factors involved in type I left ventricular rupture include extensive calcification, particularly of the posterior mitral valve annulus, mitral valve re-replacement in which the old prosthesis must be removed, and selection of a prosthesis that is too large for the ventricle [1–8]. In type II and III ruptures the mechanical injury of the ventricular wall in a patient with intrinsic myocardial disease seems to be important [3, 6]. Mechanical injury may occur during excision of the papillary muscle or as a result of excessive traction of the ventricle or mitral annulus either during or after mitral valve replacement. In some patients the specific cause may not be identified.

This complication may be prevented by preserving all or parts of the posterior leaflet apparatus of the mitral valve [6, 7]. In heavily calcified valves crushing and removing the calcium may permit placement of sutures through the remains of the leaflet and the annulus. To prevent this complication excessively large prostheses should be avoided, excessive traction on the ventricles should be avoided, and postoperative hypertension should be carefully prevented [1–8].

The mortality of left ventricular rupture after mitral valve replacement ranges from 65% to 100% [1–5]. In the few reported survivors the complication was usually recognized intraoperatively [1, 4, 5, 7–9]. Even when it is recognized early there is a high mortality due to technical difficulties encountered in repairing the ventricular tear.

The repair should be performed on cardiopulmonary bypass with the heart arrested and empty. Most reports describe repair of the tear from the outer surface of the

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heart using multiple sutures buttressed on strips of Teflon felt [1–4]. Another method includes the use of an external patch, which is placed over the entire area of ecchymosis and hematoma on the epicardial surface and sutured to healthy myocardium [4]. These repairs risk injury to the branches of the circumflex coronary artery and may necessitate aortocoronary bypass grafting to prevent myocardial infarction. Further, the epicardial and intramyocardial hematoma surrounding the tear may not permit accurate placement of the sutures to the healthy myocardium, and may therefore result in failure. The repair of type I rupture has been described using multiple pledget-supported sutures that incorporate the left atrium, the sewing ring of the mitral prosthesis, and the proximal part of the wall of the left ventricle [4, 5]. Again, with this technique the circumflex coronary artery and the coronary sinus are prone to injury.

This report describes an endocardial patch for repair of type I atrioventricular mitral annular disruption. This repair does not jeopardize the circumflex coronary artery and the coronary sinus. The repair is performed from inside the left atrium using a patch that is directly sewn to the endocardium around the tear to reinforce the mitral annulus. The mitral valve prosthesis is then secured with sutures incorporating this patch. Use of autologous pericardium for this purpose has been described [7–9]. In this patient glutaraldehyde-preserved bovine pericardium was used because satisfactory autologous pericardium was not available, as this was a redo procedure. The method is particularly useful in reconstruction of this type of extensive disruption of the mitral annulus.

Disrupted mitral annulus can be successfully reconstructed using pericardium, which is sutured directly to the endocardium around the area of the tear. This allows accurate repair.

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Amiodarone-Induced Pulmonary Mass

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Amiodarone is an effective agent in the treatment of life-threatening ventricular arrhythmias. However, there are numerous side effects associated wih this drug, including pulmonary toxicity. This report describes a pulmonary mass that developed in a patient receiving amiodarone and was initially thought to be a lung cancer. Complete resolution occurred after cessation of the drug.

(Ann Thorac Surg 1989;47:918–9)

Amiodarone is an iodinated benzofuran derivative that is extremely effective in the treatment of life-threatening ventricular rhythm disturbances. Although used in Europe since 1967, there were no reported incidences of pulmonary toxicity until 1980 after introduction of the drug in the United States.

Since then, numerous reports have appeared recognizing amiodarone pulmonary toxicity (APT) as a clinical entity. The radiographic appearance of APT is typically an interstitial or diffuse alveolar infiltrate often resembling cardiogenic pulmonary edema. We report a patient who developed a discrete apical pulmonary mass while receiving amiodarone therapy. The diagnosis of APT was made by exclusion and complete resolution of the mass occurred after discontinuation of the drug and concurrent steroid therapy.

A 53-year-old man with a history of cigarette smoking and hypercholesterolemia had experienced two previous myocardial infarctions in 1976 and 1983. The second infarct was complicated by pulmonary edema and cardiac arrest. Cardiac catherization after the second infarct demonstrated severe three-vessel coronary arteriosclerotic disease and an ischemic cardiomyopathy with an ejection fraction of 37%.

Coronary artery bypass grafting was performed in February 1984 in conjunction with resection of a left ventricular aneurysm. Postoperatively, the patient experienced recurrent ventricular arrhythmias initially responsive to procainamide, but systemic lupus erythematosis developed requiring discontinuation of this drug. Electrophysiological studies demonstrated inducible ventricular arrhythmias despite use of all antiarrhythmic agents. In July 1986, administration of amiodarone hydrochloride was begun with a loading dose of 1400 mg/day for ten days, followed by a maintenance dose of 400 mg/day.

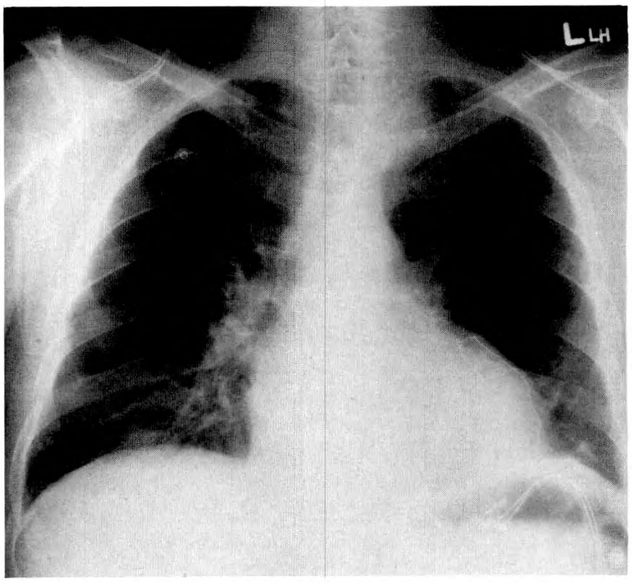

Fig 1. Chest roentgenogram at admission demonstrating left apical mass.

The patient did well until November 1987, when he was seen with a low-grade fever, a nonproductive cough, myalgias, and weight loss. Peripheral leukocyte count was normal at $10.4 \times 10^3/\mu L$; however, hepatic transaminase levels were uniformly elevated. Chest roentgenogram demonstrated a 3 × 2.5-cm density in the left apex (Fig 1), and chest computed tomography confirmed the mass (Fig 2). Pulmonary function tests were consistent with a mild restrictive pattern and decreased diffusion capacity. Percutaneous needle aspirate demonstrated inflammatory cells, and bronchoscopy with bronchial brushing under fluoroscopic control was negative for malignancy. All bacterial, fungal, and mycobacterial cul-

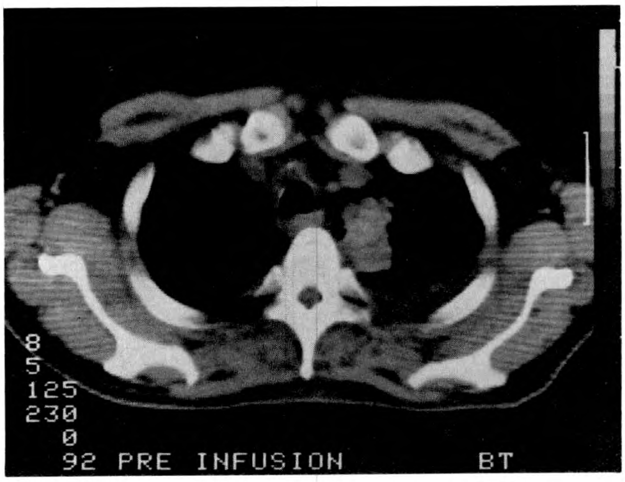

Fig 2. Computed tomography of the chest confirming left apical mass.

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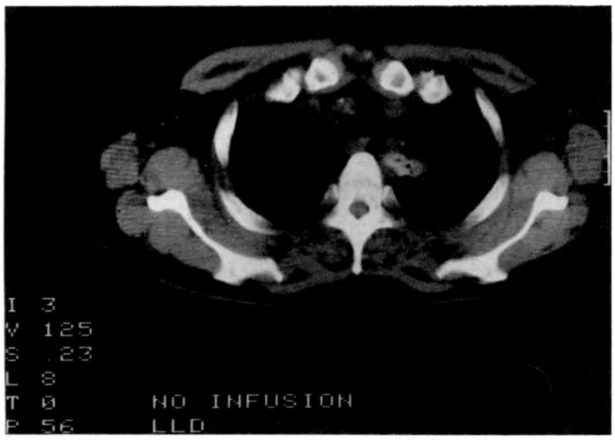

Fig 3. Computed tomography several weeks after discontinuation of amiodarone with regression of left apical mass.

tures were negative. The diagnosis of probable amiodarone-induced pulmonary toxicity was made by exclusion and the drug was discontinued; administration of prednisone, 40 mg/day, was initiated. One month later, repeat computed tomographic scan demonstrated regression of the mass (Fig 3), and serial roentgenograms over a follow-up period of almost 1 year have demonstrated complete resolution of the lesion in the left upper lobe (Fig 4).

Comment

Amiodarone is a benzofurane derivative that has been used widely in Europe as an antiarrhythmic agent since 1967. Under current Food and Drug Administration guidelines, the drug became available in the United States in 1985 for the treatment of life-threatening ventricular tachyarrhythmias [1]. There are numerous side effects, some serious, which have restricted the use of amiodarone in the US.

Amiodarone hydrochloride is absorbed slowly and is accumulated by most tissues after leaving the circulation. It is metabolized in the liver with a long mean elimination half-life estimated at 52 days [2]. The antiarrhythmic activity of the drug is not fully understood, but it principally acts by depressing the sinus node and atrioventricular node, as well as prolonging repolarization in the myocardium.

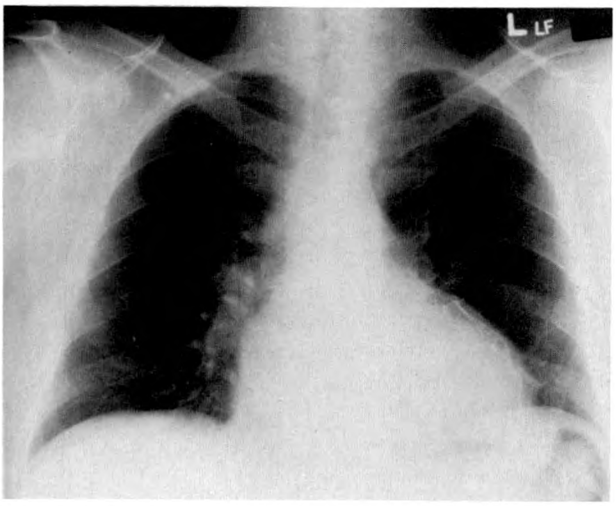

Fig 4. Chest roentgenogram several months after discontinuation of amiodarone with complete resolution of mass.

Numerous adverse side effects have limited the clinical application of amiodarone. The overall incidence of side effects ranges from 30% to 93%, and that of serious side effects (including hepatitis, pneumonitis, exacerbation of congestive heart failure, and exacerbation of arrhythmias) is 9% to 26% [2].

Clinically apparent APT occurs in 5% to 7% of patients receiving the drug. Less apparent changes in pulmonary function are usually a reduction in lung diffusion capacity, and this probably occurs in a substantially larger percentage of patients [3]. The mechanism of APT is uncertain, but probably is a complex interaction of direct toxic effects on lung tissue and an indirect inflammatory response to the accumulation of phospholipid inclusions in the alveolar cells induced by the drug. Regardless of mechanism, recent studies [3, 4] have demonstrated that the pulmonary toxicity of amiodarone relates to both the dosage and the cumulative exposure to the drug. Patients receiving 400 mg or less daily from the start of treatment rarely develop APT.

The clinical manifestation of APT is usually the insidious onset of nonproductive cough, weakness, dyspnea, weight loss, and occasionally fever. The radiographic appearance is usually a diffuse bilateral interstitial pattern, which may be difficult to discern from cardiogenic pulmonary edema (5). However, the appearance may be quite variable and asymmetric with patchy infiltrates peripherally. The case presented here is unusual for the radiographic appearance of a discrete mass at the lung apex, which resolved with the cessation of the drug and concurrent steroid therapy. A similar case of an infiltrative lesion in the right upper lobe that resolved after discontinuing amiodarone therapy was recently described in the medical literature (6).

Amiodarone pulmonary toxicity is a diagnosis of exclusion at this time, but the clinician must be aware of the extreme variability in its radiographic appearance. Appropriate diagnostic maneuvers should be done to be certain that a cancer is not present, as these patients are certainly susceptible to malignancies. This diagnosis should be considered in any patient who is receiving amiodarone and develops pulmonary parenchymal changes.

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Mediastinal Involvement by Myxoid Liposarcoma

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Metastatic involvement of the mediastinum by liposarcoma is uncommon, and clinical experience in its management is limited. A patient with liposarcoma of the lower extremity having a concomitant anterior mediastinal mass as the only manifestation of distant metastatic involvement is described.

(Ann Thorac Surg 1989;47:920–1)

Pulmonary parenchymal metastases frequently occur in soft tissue sarcomas because of hematogenous dissemination. Lymph node involvement as a route of local, regional, or distant metastatic spread is distinctly uncommon among all histological subtypes of soft tissue sarcomas [1, 2]. Myxoid liposarcoma has a predilection for metastatic involvement of serosal surfaces [1]. We report a patient with an extensive low-grade liposarcoma of the lower extremity with an unusual, concomitant solitary anterior mediastinal metastasis.

A 43-year-old woman was seen with a slowly enlarging posterior thigh mass. A smaller mass located at the same site had been removed at another institution 23 years earlier. This was reported to have been a lipoma. The patient denied weight loss or pulmonary symptoms. Physical examination demonstrated a right posterior thigh mass measuring 30 × 30 cm. Neurovascular function was intact. Cardiovascular examination was normal, with no clinical signs suggestive of superior vena caval syndrome. There was no lymphadenopathy. Chest roentgenogram on admission revealed a soft tissue mass in the anterior mediastinum (Fig 1). Computed tomographic scan of the thorax demonstrated a 5 × 5-cm anterior mediastinal mass with normal pulmonary parenchyma (Fig 2).

Marginal excision of the thigh mass, as defined by Enneking and associates [3], was accomplished and interstitial afterloading catheters were placed within the tumor bed for postoperative brachytherapy. Low-grade myxoid liposarcoma was documented pathologically.

En bloc resection of the mediastinal mass and the thymus gland was performed via a median sternotomy 2 weeks later. A 5 × 7 × 8-cm friable mass with a pseudocapsule was encountered between the pericardium and left pleura that was attached to but not invading the thymus gland. This proved to be a grade 1 myxoid liposarcoma with histological characteristics identical to those of the thigh lesion (Fig 3). Two lymph nodes

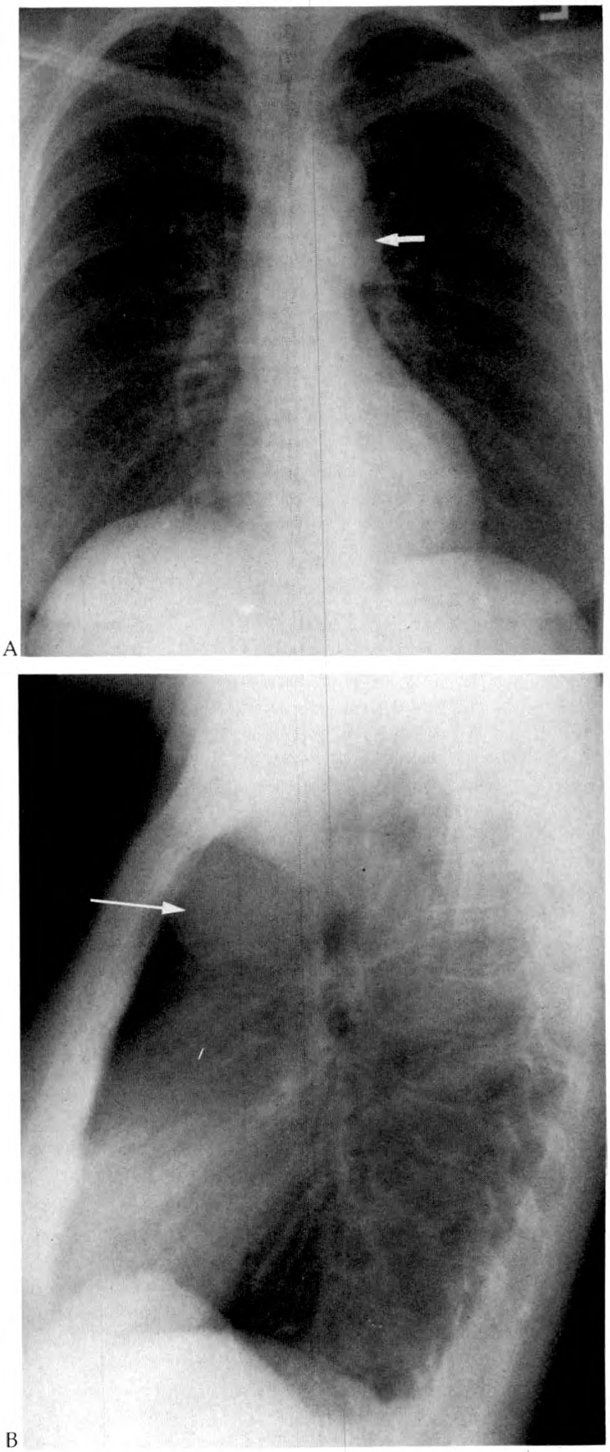

*Fig 1. Posteroanterior (A) and lateral (B) chest roentgenograms showing the anterior mediastinal mass (*arrow*).*

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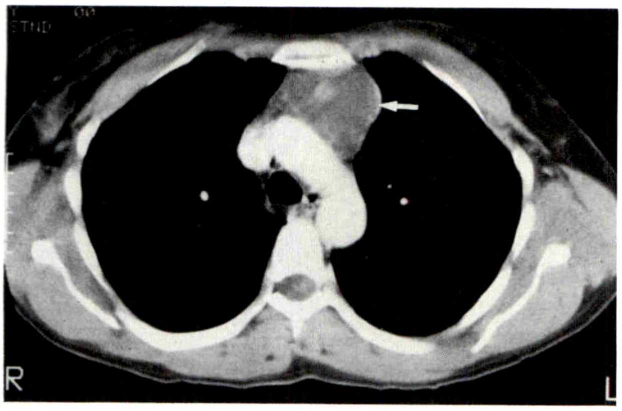

Fig 2. Anterior mediastinal mass (arrow) *on computed tomographic scan.*

biopsied revealed only sinus histiocytosis. Consolidative irradiation (4,550 cGy) was delivered to the mediastinum. Thirteen months later the patient remains free of disease.

Comment

Liposarcoma is primarily a tumor of adult life and most frequently involves the thigh or retroperitoneum. Typically the lesion achieves a large size, and pseudocapsule formation is observed [1, 2, 4]. Pathologically, liposarcoma is categorized into four groups: myxoid, round cell, well-differentiated, and pleomorphic. Myxoid liposarcomas account for 40% to 50% of the histological subtypes. Metastatic involvement in any histological subtype usually involves the lung.

The biological behavior of liposarcoma is related to the size, location, and histological subtype of the primary tumor [1]. Recurrence rate is influenced more by the location of the tumor than by its histological type. The reverse is true for metastasis [1]. Recurrence may be delayed for many years after the initial therapy [1]. The term *atypical lipoma* has been applied to well-differentiated liposarcomas with low recurrence rate [5]. It is quite possible that the original tumor in our patient was a so-called atypical lipoma that was misdiagnosed as a lipoma.

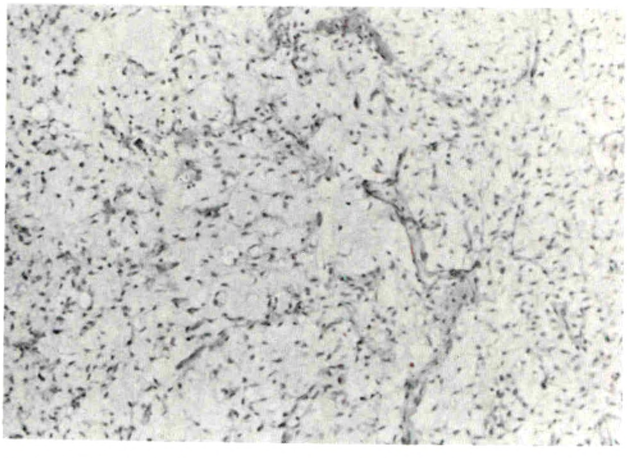

Fig 3. Typical "chicken-track" pattern of vascularization with spindle-shaped and stellate cells within a loose myxomatous stroma. (Hematoxylin and eosin, ×100 before 50% reduction.)

Primary mediastinal involvement by sarcoma is distinctly rare [6]. Only 7 cases of malignant mesenchymal tumors were noted in a series of 400 cases of resected mediastinal neoplasms reported by Davis and co-workers [7]. Metastatic involvement of the mediastinum by liposarcoma, on the other hand, is more common [4]. For unknown reasons, myxoid liposarcomas tend to metastasize to serosal surfaces of pleura, pericardium, and diaphragm, either alone or in combination with involvement of other viscera [1]. To our knowledge, our patient is unique in that neither pleura nor percardium was involved with the tumor mass.

Because of the low incidence of mediastinal sarcomas, treatment strategies are extrapolated from sarcomas of other sites of origin. If the tumor is resectable, total excision followed by irradiation has been advocated to minimize risk for local recurrence [4]. Postoperative irradiation of sarcoma involving the extremities after surgical excision has yielded 5-year cure rates of greater than 85% as compared with 66% after radical surgical resection alone [6]. Mediastinal lymphadenectomy is not recommended because of the low incidence of nodal involvement with serosal metastases [1, 2]. The role of systemic chemotherapy is yet to be determined, although based on the experience with limb lesions, consideration could be given to the addition of chemotherapy in high-grade histologies or incompletely resected lesions [8]. Whether such therapy will have a positive impact on survival is unknown at this time.

Isolated metastatic involvement of the mediastinum by liposarcoma is an uncommon condition, and experience in clinical management is limited. To date, treatment strategies have been extrapolated from lesions of the extremities. A multiinstitutional trial is suggested to better define treatment strategies for this disease.

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Late Postoperative Cardiac Tamponade Presenting as Dysphagia

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A case of late cardiac tamponade seen with progressive dysphagia 15 days after aortic valve replacement is reported. The diagnosis was confirmed echocardiographically and successful pericardiocentesis was followed by immediate alleviation of the dysphagia.

(Ann Thorac Surg 1989;47:922–3)

Late postoperative tamponade after an open heart operation is an uncommon, potentially fatal complication [1]. It may be seen 1 week to 6 months postoperatively [2], and is usually associated with nonspecific symptoms [3]. We report successful treatment of a case of late postoperative tamponade seen with progressive dysphagia.

A 50-year-old man suffering from rheumatic aortic incompetence underwent aortic valve replacement with a porcine xenograft at the University Hospital of Wales in October 1987. A single anterior mediastinal chest tube was used postoperatively with blood drainage of 700 mL before its removal. The patient was discharged home eight days after operation in a satisfactory condition, with the heart in sinus rhythm. Oral anticoagulants were not employed.

One week after discharge the patient was readmitted urgently with a three-day history of feeling generally unwell. He complained of upper abdominal discomfort and worsening dysphagia, initially for solids only, but later also for liquids, during the 24 hours before admission.

On examination, he appeared ill, pale, and peripherally vasoconstricted. He was afebrile. The heart rate was 100/minute and irregular. The blood pressure was 110/60 mm Hg with 15 mm Hg of pulsus paradoxus. The jugular venous pressure was elevated 6 to 8 cm H_2O above normal. Auscultation revealed normal heart sounds and a short systolic murmur. Abdominal examination was normal.

The hemoglobin level was 9.7 g/dL and the urea level, 12.7 mmol/L. Serum amylase was normal. An electrocardiogram showed atrial fibrillation with normal-size complexes. A chest roentgenogram showed an enlarged, globular heart shadow compared with preoperative and postoperative radiographs. Two-dimensional echocardiography revealed a large pericardial effusion both anterior and posterior to the heart (Fig 1).

Emergency pericardiocentesis was performed, under fluoroscopic control, via the subxiphoid route. Seven hundred milliliters of heavily blood-stained fluid was aspirated. A pigtail catheter left in situ drained 600 mL more during the subsequent 24 hours. The patient's clinical condition improved dramatically, with immediate resolution of the dysphagia. In addition, the heart spontaneously reverted to sinus rhythm.

A repeat echocardiogram performed five days later revealed minimal pericardial effusion. The patient was discharged home and remains well 6 months postoperatively.

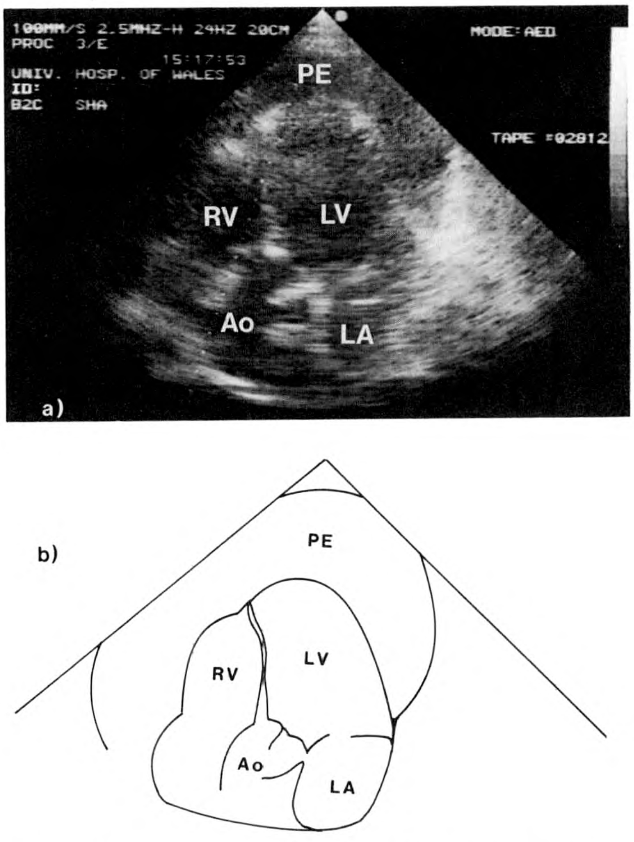

Fig 1. (a) Two-dimensional echocardiogram showing a large pericardial effusion. (b) An explanatory diagrammatic representation. (Ao = *aortic root;* LA = *left atrium;* LV = *left ventricle;* PE = *pericardial effusion;* RV = *right ventricle.)*

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Comment

Pericardial effusion after an open heart operation may be demonstrated echocardiographically in more than 30% of patients [4]. Despite this, cardiac tamponade in the early postoperative period occurs in only 3% to 6% of cases [1, 5]. Late tamponade, which has been reported as late as 6 months after operation [2], is rare (1%) [3, 6]. Mortality is substantial (16% to 35%) and has been attributed to delayed diagnosis and treatment [1, 5].

The pathogenesis of late tamponade is thought to be related to breakdown of residual thrombus, which expands hydrophilically within the pericardial space [3]. Oral anticoagulants [2, 6] and the postpericardiotomy syndrome [2] have been implicated by some authors as possible etiological agents. We have recently shown that postoperative effusion and late tamponade is increased when a single anterior mediastinal chest tube is used as opposed to an anterior and a posterior drain [4].

Late cardiac tamponade usually is seen with a variety of nonspecific symptoms including malaise, fever, chest and upper abdominal pain, and dyspnea [3]. Diagnosis may be made from physical findings, but echocardiographic confirmation is usual and cardiac catheterization is sometimes required [5]. Dysphagia is well recognized as a symptom of pericardial disease [7] and left atrial enlargement [8] but, to our knowledge, has been recorded as a symptom of late tamponade in only 2 patients [3]. Dysphagia may be explained by the displacement and compression of the esophagus posterior to the enlarged pericardial cavity. In addition, spontaneous reversion of the heart to sinus rhythm after evacuation of the effusion confirms the association of supraventricular arrhythmias with postoperative effusion, recently reiterated by ourselves [9].

With this report we wish to emphasize that, although dysphagia as the presenting symptom of late postoperative tamponade is rare, its recognition should alert the physician to the possibility of this serious yet eminently treatable complication of open heart operations.

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Traumatic Laceration of a Saphenous Vein Graft: Successful Surgical Repair

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Traumatic laceration of a saphenous vein grafted for coronary artery bypass is extremely rare. Successful surgical repair of a laceration was performed in a 64-year-old man who developed retrosternal hematoma from a saphenous vein graft after blunt injury to the chest.

(Ann Thorac Surg 1989;47:924–5)

Since the introduction of direct surgical revascularization of the ischemic myocardium by Favaloro in 1969 [1], the autogenous saphenous vein graft has been used widely as a bypass graft conduit. Only a few cases of saphenous vein graft rupture have been reported [2–4], and traumatic laceration of the vein graft is extremely rare. We report here a case in which a traumatic laceration of the saphenous vein graft was successfully repaired.

A 64-year-old man with exertional angina underwent uncomplicated coronary artery bypass grafting on September 9, 1981. After a reverse saphenous vein graft was placed to the left anterior descending coronary artery, the patient remained asymptomatic until May 1988, when he fell off his motorcycle and bruised his anterior chest. Three weeks later, he was admitted to a local hospital for persisting dull retrosternal pain and a 4 × 4-cm subcutaneous soft, tender mass below the previous operative scar in the xiphoid. Under the tentative diagnosis of subcutaneous abscess, he was transferred to our hospital for further evaluation.

On admission, the patient was moderately uncomfortable and physical findings were unremarkable. Chest roentgenograms and electrocardiograms were nondiagnostic. Puncture of the anterior chest mass revealed bloody fluid. Computed tomography revealed two separate masses: an anterior chest mass corresponding to the subcutaneous hematoma and a 3 × 11-cm hematoma underneath the sternum (Fig 1). The connection between these two hematomas was unclear. Cineangiography of the saphenous vein graft revealed extravasation of the contrast media 2 cm distal to the aortic anastomosis of the graft (Fig 2). The diagnosis was retrosternal hematoma, which had been caused by bleeding of the saphenous vein graft but confined by postoperative pericardial adhesion.

As the patient's hematocrit was decreasing progressively, an emergency operation was performed. Before median sternotomy, an intraaortic balloon pump was inserted and femoral artery–femoral vein cardiopulmonary bypass with normothermia was instituted. Immediately after median sternotomy, there was massive bleeding from the mediastinum. Because of pericardial adhesion and massive bleeding, it was extremely difficult to expose the bleeding site. However, under extracorporeal circulatory assistance, the retrosternal hematoma was removed and the saphenous vein graft was dissected and exposed, revealing a 3-mm longitudinal laceration in the vein graft with no aneurysmal change or evidence of infection. A bacterial culture taken intraoperatively was negative. Using temporary clamps on the proximal and distal sides of the laceration, the laceration was closed by four interrupted 7-0 nonabsorbable sutures.

Postoperative hemodynamics were stable and the intraaortic balloon pump was withdrawn on the following day. The patient's recovery was hampered by liver dysfunction due to preexisting liver cirrhosis and blood transfusion during the second operation, but he was discharged from the hospital without any complications.

Comment

Various types of blunt trauma to the chest have been shown to cause injury to the heart [5]. Nonpenetrating trauma to the heart may cause pericardial rupture, myocardial contusion, rupture of the cardiac wall or valves, or

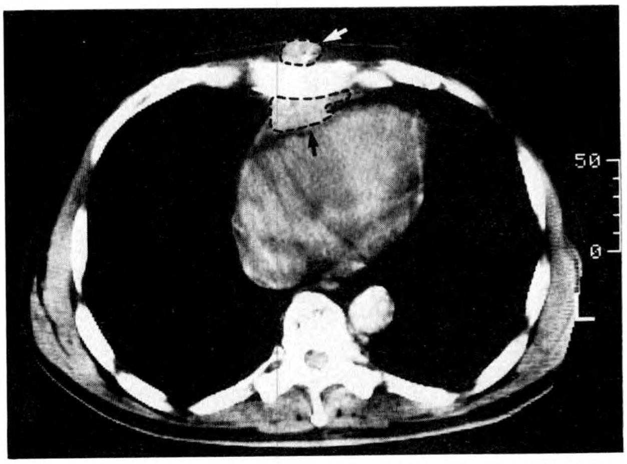

*Fig 1. Preoperative computed tomography of the thorax revealed retrosternal hematoma (*black arrow*) and subcutaneous hematoma on the anterior chest wall (*white arrow*).*

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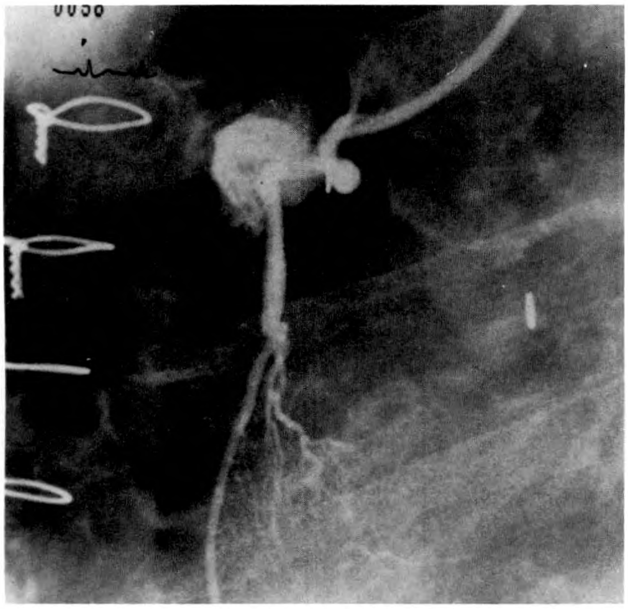

Fig 2. Preoperative angiogram of the saphenous vein graft demonstrated extravasation of the contrast media from the vein graft 2 cm distal to the proximal anastomosis in the aorta.

rupture of coronary arteries. However, traumatic laceration of the saphenous vein graft after coronary artery bypass grafting is extremely rare, and to our knowledge, this is the first reported case. Most often, the rupture of a saphenous vein graft is caused either by aneurysmal change, infection, or fistula of the vein graft [2–4]. Our patient complained of retrosternal pain only after an episode of blunt injury to his anterior chest. No evidence of aneurysmal change or infection in the vein graft was found at the time of operation. Therefore, we believe that the rupture of this patient's saphenous vein graft was caused by the preceding blunt injury to his chest. Bleeding from the graft was fortunately confined by pericardial adhesion, forming a retrosternal hematoma that gradually extended to the subcutaneous tissue in the anterior chest.

Shapeero and associates [2] performed catheter embolization in a patient with rupture of a coronary bypass graft aneurysm. However, embolization was inappropriate in our case, because the vein graft fed viable myocardium. Therefore we chose direct surgical repair of the graft through median sternotomy. Because we anticipated the need for decompression of the heart to expose the bleeding site and temporary clamping of the graft to repair the laceration, we used femoral–femoral bypass for decompression and an intraaortic balloon pump for myocardial protection during temporary clamping. As a result, the graft laceration was successfully repaired despite massive bleeding from the mediastinum and recalcitrant pericardial adhesion.

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New Clamp for Intraoperative Chest Tube Placement

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We describe an instrument designed specifically to avoid the pitfalls of intraoperative chest tube placement.

(Ann Thorac Surg 1989;47:926)

Placement of chest drainage tubes after thoracotomy can be a minor but frequent annoyance. Instruments such as Kelley, Schnidt, and Pean clamps have jaws that are often inadequate for firmly grasping noncompressible vinyl catheters. In addition, hinged instruments require an entry wound and intercostal tract considerably larger than the catheter to achieve sufficient opening of the jaws. These problems are magnified when the chest tube entry site is some distance from the thoracotomy and also with the smaller incisions that are gaining in popularity.

A new instrument has been devised to facilitate operative chest tube placement (Scanlan International, St. Paul, MN). It is made of stainless steel and has an effective intrathoracic length of 18 cm. The tip is pointed and the shaft gently curved to allow easy insertion and intrapleural maneuverability (Fig 1). In the midportion of the instrument is a circumferential steel loop which prevents separation of the shafts when full pressure is applied to the handles. The teeth are sharp and directed backward to prevent slipping of the catheter as it is withdrawn from the chest (Fig 2). A small pin and opposing hole add further security against slippage. The jaws open and close by a sliding action. This feature permits the use of a smaller stab wound than that necessary with hinged instruments.

Since we began using this clamp, we have not had to struggle to stretch the chest tube tract, fumble to locate and grasp the drain with the barely opened jaws of a hinged instrument, or face the annoyance of losing the catheter as it is withdrawn through the chest wall. The instrument may also be useful for tunneling grafts and vascular access devices.

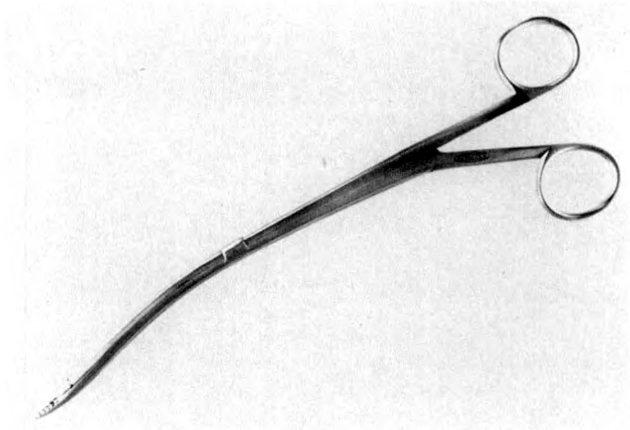

Fig 1. Specially designed chest tube clamp.

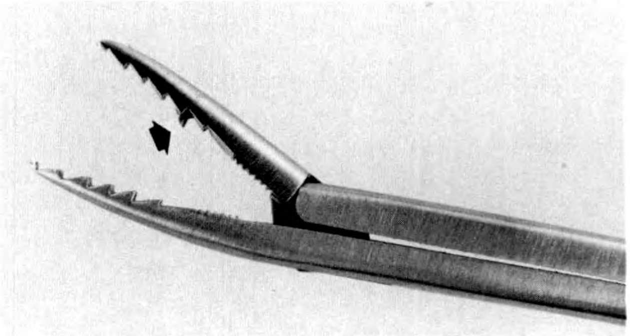

Fig 2. Close-up to show jaws and pin (arrow).

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Interlocking Figure-of-8 Closure of the Sternum

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Sternal dehiscence and mediastinitis are two of the most severe complications of a median sternotomy. A technique of closure is described that appears to provide a more stable sternal approximation without any increase in overall complication rate. Using this technique in 978 consecutive patients, no cases of sternal dehiscence or mediastinitis have been seen.

(Ann Thorac Surg 1989;47:927–9)

Median sternotomy has become the standard approach to the heart and great vessels in most cardiac procedures. It has also gained application for pulmonary resections in patients with bilateral lesions or poor pulmonary function. Indications for operation in both cardiac and pulmonary operations have been extended to include older and higher risk patients with osteoporosis, malnutrition, chronic lung disease, obesity, low cardiac output, and other systemic illnesses. As a result, the variety and severity of sternal complications have increased. Major wound complications, including major wound abscesses, chronic osteomyelitis, costal chondritis, sternal dehiscence, and mediastinitis, occur in 0.97% to 1.86% of cases [1–6]. These complications have a mortality rate of 19% to 39% [1, 2, 4, 6]. The most important factor in preventing the major complications, particularly sternal dehiscence and mediastinitis, is a stable sternal approximation.

There have been numerous articles published on techniques of sternal closure designed to achieve maximum sternal stability [7–13]. Each technique has some merit and usefulness. It appears that there are two crucial technical factors that are common to the successful closure of sternotomies, even in complicated settings. First is the use of the figure-of-8 suture technique to avoid direct perpendicular shearing forces of the wire [8, 13]. The figure-of-8 allows for both an oblique and horizontal angle of force, which is less likely to loosen or fracture than a simple closure, which applies tension purely in a horizontal plane through the sternum. The second factor is some method to reinforce the lateral table of the sternum [7–13]. This reinforcement allows for a tighter closure of the sternum and lessens the likelihood of the wires cutting through when placed in a peristernal fashion.

A combination of the lateral horizontal weave of Robicsek and associates [11] and interrupted figure-of-8 sutures has been very successful in cases of reclosure for sternal dehiscence. However, this technique would be somewhat cumbersome and time consuming for routine closure of all sternotomies. In an effort to streamline the closure but adhere to the concepts of lateral reinforcement and oblique forces for approximation, a technique of interlocking figure-of-8 sutures is described.

Technique

The closure is performed entirely with No. 5 stainless steel wire. The manubrium is first stabilized by placing two simple transmanubrial sutures, one at the level of the sternoclavicular joint and the other approximately 1 to 2 cm inferiorly. After completion of the transmanubrial sutures, the next wire is passed through the first and second interspaces in a figure-of-8 manner that crosses beneath the sternum, leaving the horizontal loops of the suture on the exterior surface of the sternum (Fig 1). The second figure-of-8 suture is performed identically to the first except it passes through the second and third interspaces. This series is continued until the end of the sternum is reached. The wires are then pulled tight using a sternal approximator or by twisting according to the preference of the surgeon.

Except for the transmanubrial wires, all other wires are placed in a peristernal figure-of-8 manner. Closure of the sternum requires two simple transmanubrial wires plus four figure-of-8 wires. Depending on the shape and length of the sternum, additional or fewer wires are needed. The resulting closure then has two wires through each interspace. It is important to be sure the wires overlap in each interspace; the upper loop of each subsequent figure-of-8 is placed superior to the lower loop of the previous wire (see Fig 1). As each wire is tightened the superior loop of the figure-of-8 interlocks with the inferior loop of the previously placed suture. This interlocking technique imparts lateral reinforcement to the closure. Furthermore, by having two wires in each interspace the compressive force is applied over two points per interspace. It appears that this prevents sternal fracture by distributing the same force over two wires instead of one and by dispersing the tension over a greater area of each interspace.

To gain full benefit of this technique, the wires must be pulled up securely to eliminate any redundancy behind the sternum. It is also important to place each pass of the peristernal figure-of-8 wire close to the cortex of the sternum to avoid damage to the internal mammary artery lying laterally.

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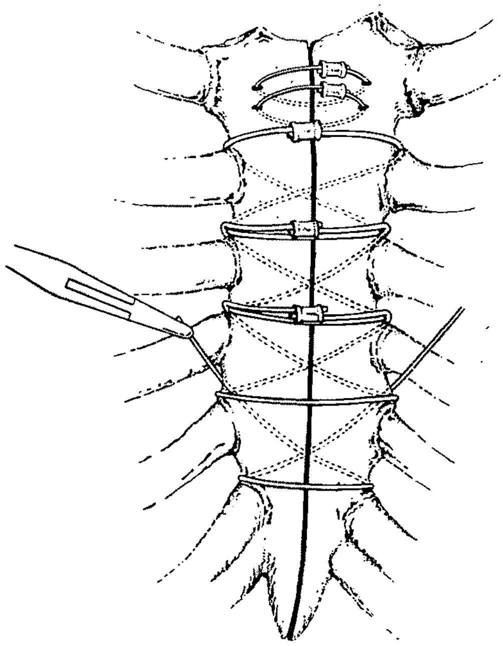

Fig 1. Closure of the sternum using interlocking figure-of-8 sutures.

Results

We have employed this technique of interlocking figure-of-8 peristernal closure in all patients who had a median sternotomy incision since August 1986. In the interval between August 1, 1986, and December 23, 1987, a total of 978 patients underwent cardiac procedures performed by five surgeons; each operation used a median sternotomy incision and was closed using the technique discussed. Sternal wound infections occurred in 24 patients, resulting in a postoperative infection rate of 2.45% (Table 1).

Of these 24 patients, 9 patients were considered to have major complications as defined by the need for further surgical intervention. The treatment for all 9 patients included prompt sternal wire removal and muscle flap closure. In no instance did any patient develop either mediastinitis or sternal dehiscence. The remaining 15 patients had minor wound infections and all healed by secondary intention. Thus, the major and minor sternal wound complication rate was 0.92% and 1.53%, respectively. Reclosure of the sternum was not required in any patient during the 17 months our study encompassed. Excessive or unusual postoperative pain has not occurred. There were also no episodes of mediastinal hemorrhage secondary to internal mammary artery injury in this study group.

Comment

The interlocking figure-of-8 closure provides a secure and stable closure of the sternum. Although the major sternal wound complication rate of 0.92% is comparable with the results found in other studies, it is noteworthy to mention that there were no instances of sternal dehiscence or mediastinitis in this study group. It is our opinion that the added stability provided by this closure has accounted for the absence of sternal dehiscence and mediastinitis in our patient population. This method of closure has proved to be reliable for both routine and high-risk patients. From a practical standpoint it is easily mastered and requires no additional time or equipment. This technique is currently our routine form of closure on all patients.

Table 1. Patients With Complications After Interlocking Figure-of-8 Sternal Closure

Patient No.	Sex	Age (yr)	Procedure	Closure
1	F	66	MVR	PM flap
2	F	62	CABG, LVA	LD flap
3	M	71	CABG	PM flap
4	M	60	CABG	SI
5	M	65	CABG	LD flap
6	F	40	MVR	SI
7	F	70	AVR	SI
8	M	59	CABG	SI
9	M	76	MVR	SI
10	M	74	CABG	PM flap
11	M	49	CABG	SI
12	M	60	CABG	PM flap
13	F	67	AVR	LD flap
14	M	67	MVR	SI
15	F	54	AVR, MVR	SI
16	M	73	CABG	SI
17	M	42	CABG	SI
18	M	68	CABG	LD, PM flap
19	M	65	CABG	SI
20	F	64	CABG	SI
21	F	61	CABG	SI
22	M	77	CABG	LD flap
23	M	52	CABG	SI
24	M	73	CABG	SI

AVR = aortic valve replacement; CABG = coronary artery bypass graft; LD = latissimus dorsi; LVA = left ventricular aneurysm repair; MVR = mitral valve replacement; PM = pectoralis major; SI = secondary intention.

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REVIEW OF RECENT BOOKS

Treatment of End-Stage Coronary Artery Disease
Edited by P. J. Walter
Basel, Switzerland, Karger, 1988
305 pp, illustrated, $126.00

Reviewed by John E. Connolly, MD

From June 10 to 12, 1987, an international symposium entitled "Treatment of End-Stage Coronary Artery Disease" was held in Antwerp, Belgium. Forty-one separate presentations were made by an international group of cardiac surgeons and are published in this book.

The symposium addressed four topics: treatment of diffuse coronary artery disease by endarterectomy, reoperation for recurrent coronary artery disease, treatment of evolving and completed myocardial infarction, and staged heart transplantation for end-stage coronary artery disease.

Although endarterectomy was widely employed 20 years ago when coronary artery surgery started, it was soon replaced by conventional bypass grafting. Eleven separate papers deal with the recent revival of the use of extensive coronary artery endarterectomy in patients who are not candidates for conventional bypass. The results of such extensive endarterectomy are shown to compare favorably with the only other alternative treatment for this type of patient; namely, heart transplantation.

Several papers point out that although extensive coronary endarterectomy carries a higher rate of myocardial infarction and mortality than conventional bypass, a combined procedure can give otherwise inoperable patients substantial benefit and is therefore indicated in select patients. Several papers suggest that the future place for coronary artery endarterectomy may lie in the use of lasers, especially the Excimer laser, rather than conventional techniques.

Twelve authors present papers concerning coronary artery reoperation. Redo operation is generally necessary because of progression of disease in previously unaffected arteries or occlusion or stenosis of vein grafts due to the development of arteriosclerotic disease in the vein grafts. Although mortality and morbidity of redo operations generally exceeds that of primary operation, increasing technical experience with repeat procedures has resulted in acceptable results. Emphasis is also made for the use of the internal mammary artery during initial myocardial revascularization to reduce the need for later reoperation.

Nine papers are presented that address the treatment of evolving and completed myocardial infarction. These include up-to-date expectations of thrombolytic therapy. Discussion of the addition of percutaneous transluminal coronary angioplasty to thrombolytic therapy is also presented. Other authors present the optimal subset of patients who will benefit from acute revascularization; namely, those with failed or complicated angioplasty with acute vessel occlusion. In summary, attempts to provide early myocardial reperfusion by various techniques appear to be superior to conventional therapy.

Finally, the text concludes with nine papers discussing the various aspects of heart and heart-lung transplantation. These include discussion of the use of left ventricular assist devices, biventricular assist devices, or the Jarvik heart as a bridge to transplantation.

In summary, this text of short, concise articles provides much up-to-date information for the cardiac surgeon from an international panel of experts.

Irvine, California

Allograft Aortic Valve Replacement for Bicuspid Aortic Valves With 180-Degree Coronary Ostia

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Congenital bicuspid aortic stenosis is often an indication for aortic valve replacement in young adults and children. However, when the coronary ostia are exactly 180 degrees opposite each other, placing a trileaflet human allograft with freehand technique can be difficult. The described technique enlarges the left ventricular outflow tract beginning at the annulus level, using only allograft tissue. In addition to allowing placement of a larger allograft, this method rotates the coronary ostia toward each other, converting the aortic root to three-sinus anatomy.

(Ann Thorac Surg 1989;47:930–2)

Advantages to allograft transplants for aortic valve replacement are becoming increasingly apparent. These include no need for anticoagulation; excellent hydraulic performance, particularly in small aortic roots as compared with either xenograft or mechanical prostheses; decreased frequency of thromboembolic and infectious complications; and possibly increased durability with cryopreserved allografts as compared with fresh wet stored homografts or heterografts [1]. These characteristics are particularly appealing in younger patients. Patients with congenital bicuspid aortic valve disease are often seen earlier in life and also tend to have smaller aortic annuli. When the coronary ostia are exactly 180 degrees opposite each other, there is technical challenge in inserting a normal trileaflet allograft aortic valve. Simply deviating the allograft pillars to accomodate the coronary ostia is geometrically unsound and will usually result in valve incompetence and technical failure. Some authors have suggested 180-degree ostia to be a contraindication to the use of a homograft.

My colleagues and I approach aortic valve replacement with allograft conceptually as a reconstruction of the left ventricular outflow tract rather than as an implantation of a device. Use of the principles of annuloplasty and aortoplasty to reconstruct the architecture of the aortic root with aortic allografts has been applicable in some combination in about 50% of our "freehand" allograft aortic valve replacements (not aortic root replacements). This approach also solves the problem of 180-degree ostia in a fundamentally sound way from the standpoint of semilunar valve function and aortic root geometry.

Technique

The aortotomy is performed keeping the transverse part of the incision well above the level of the expected location of the allograft pillar between the noncoronary and coronary cusps (ie, to the right of the right coronary ostium) (Fig 1). The incision is extended across the annulus posterior to the right fibrous trigone of the mitral valve and, when necessary, into the anterior leaflet. The incision is extended as far as necessary to obtain the required enlargement of the annulus. If this is well into the anterior mitral leaflet, then the left atrium is by necessity opened and requires closure. If the incision is extended just into the hinge point of the anterior leaflet, opening the atrium can often be avoided by simply dissecting the reflection of the left atrium off the base of the aorta.

The diseased native valve is excised and calcified material debrided. The annulus is sized with a Hegar dilator and the required enlargement of the annulus is accomplished, usually increasing diameter by 7 to 10 mm to achieve an "annulus" of 22 mm or greater. This enlargement, beginning at the base of the aortic root, shifts the 180-degree coronary ostia toward each other (see Fig 1).

An allograft valve is selected with an internal diameter that is 3 mm smaller than the enlarged internal diameter of the annulus. The allograft is prepared with a long flange extending on the side of the donor aorta noncoronary sinus (Fig 2). It is then inserted with a continuous proximal suture line technique accomplished with three equidistant 4-0 polypropylene sutures, each limb run to each other. These are placed taking care to align the new right and left sinuses with the rotated positions of the right and left coronary ostia. When the mitral incision is lengthy, interrupted pledgetted sutures are used for that portion and three continuous sutures run to each other for the "annulus" level of the suture line. This proximal suture line is facilitated by inverting the allograft through itself into the left ventricular cavity during the continous suture placement. Enlarging the annulus causes the enlargement of the aortic outflow to begin at the base of the aortic root, allowing a shifting of the coronary ostia into their new sinuses. This avoids distortion of the allograft pillars, which should always be sewn parallel to the outflow without deviation (Fig 3). The aortic root is enlarged in a smooth and continuous fashion by using the flange of the allograft to fill the aortotomy (augmentation aortoplasty). This accomplishes a cylindrical reconstruc-

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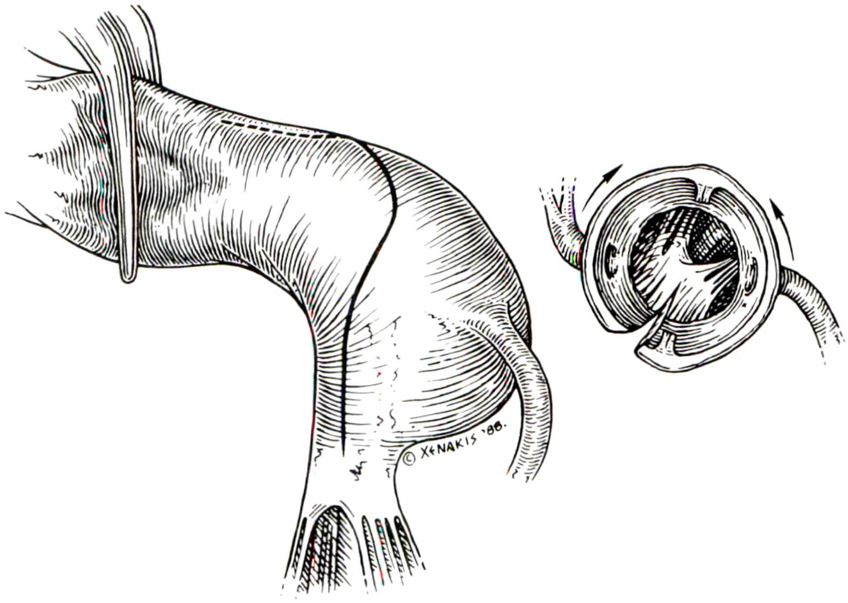

Fig 1. (Left) Aortotomy incision with the transverse portion high above the level of intended allograft pillar placement to the right of the right coronary ostium. The incision extends across aortic mitral continuity posterior to the right fibrous trigone of the mitral valve. (Right) Enlargement of the entire aortic root "shifts" the coronary ostia toward each other and leftward.

tion of the aortic root from the base of the allograft valve to above the new sinus ridge. The aortotomy closure begins at the base of the aorta at the annulus level at each side of the mitral–annulus junction as an edge-to-"flange" suture line, which makes a transition to edge-to-edge above the level of the new sinus ridge. The left atrial roof is closed with pledgetted sutures.

Comment

In 38 allograft aortic valve replacements for left ventricular outflow tract reconstructions, we have needed to use this technique five times. There have been no technical difficulties in any of the patients. All patients have normal allograft aortic valve function at postoperative Doppler echocardiographic study. None have clinically significant aortic insufficiency murmurs at short-term follow-up (longest follow-up, 24 months). There have been no operative complications.

Our technique is, in a sense, the geometric opposite of the extended aortic root replacement as described by McKowen and colleagues [2]. For tunnel stenosis, we also use their method, but for just enlargement of annulus and aorta, we find this "flange" method quicker and simpler. In this application, the enlargement is primarily for the purpose of rearranging the coronary ostial geometry, but secondarily enlarges the left ventricular outflow tract. Enlarging in the area of the "noncoronary sinus" causes the relationships of the recipient coronary ostia to the new sinuses to be realigned to trileaflet anatomy. Our technique enlarges the aortic root beginning at the annulus level, then continues contouring (enlarging as necessary) the supraannular aortic root so as to maintain parallel allograft pillars. This is similar in concept to the enlarge-

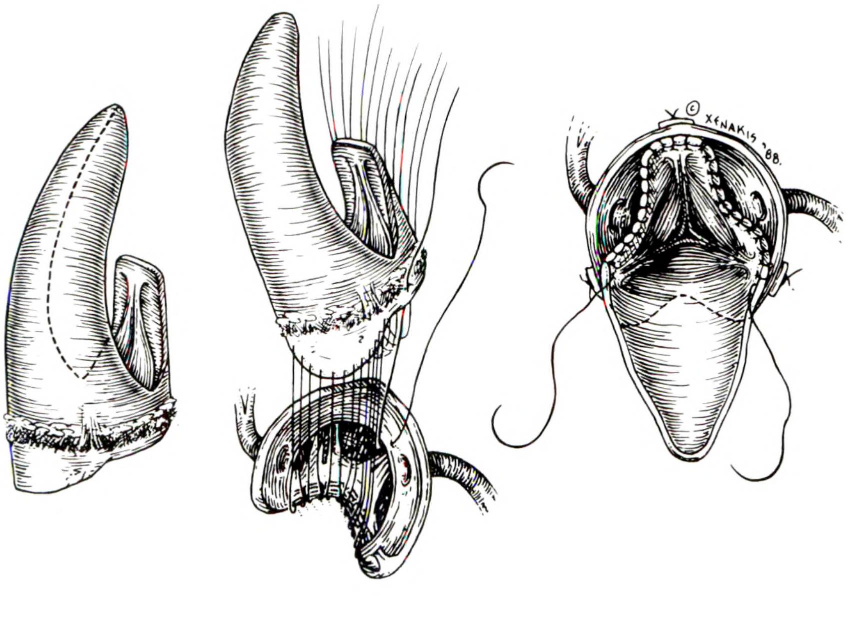

Fig 2. (Left) The allograft is trimmed with an aortic "flange" extending from the pillars on either side of the noncoronary sinus and with a "flange" of anterior leaflet mitral valve below. (Middle) Proximal suture line constructed with 4-0 polypropylene running suture except for mitral-to-mitral leaflet closure, where pledgetted interrupted sutures are used. (Right) Distal suture line with pledgets placed outside the aorta at the summit of each pillar.

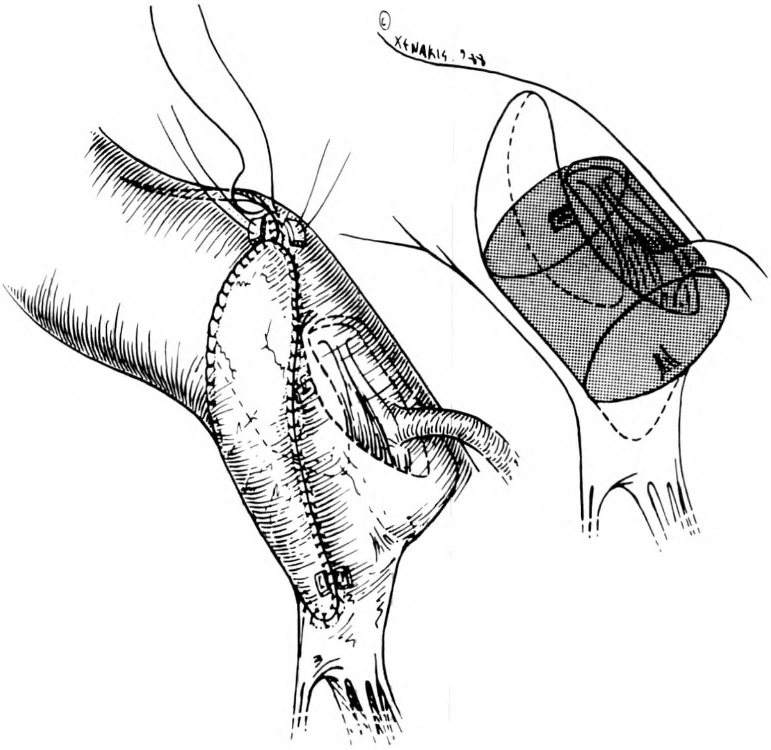

Fig 3. (Left) Aortotomy closure completed. The suture line makes a transition to edge-to-edge above the new sinus ridge. (Right) "Cylindrical" reconstruction avoiding splaying or deviation of allograft pillars. Sinus ridge diameter is similar to "annulus."

ment aortic aortoplasty described with patch material by Kirklin and Barratt-Boyes [3]. The annulus enlargement, when minor, is similar to that described by Nicks and associates [4]. When the annulus enlargement needs to be greater than 3 mm the incision into the mitral valve can be placed more posterially and extended further into the anterior leaflet of the mitral valve as described originally by Manouguian and Seybold-Epting [5].

The allograft aortic valve is particularly appealing for children and young to middle-aged adults with congenital aortic stenosis. When there is severe hypoplasia at the annulus and aortic levels, concomitant high-grade subvalvular stenosis (tunnel), or severe distortion from previous operations, then allograft aortic root replacement is a better reconstruction. When moderate hypoplasia and 180-degree coronary ostia are present this modified freehand technique is less destructive and may make future operations easier. The reconstruction of the aortic root in the fashion described can normalize aortic valve hemodynamic function and left ventricular outflow tract architecture.

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Unterdruck and Überdruck, 1904

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At the beginning of the 20th century, elective surgery within the chest was not possible; to open the pleural cavity under anesthesia meant death to the patient in almost all cases. The few exceptions to this rule—resulting from diffuse pleural adhesions or brief duration of surgical pneumothorax in robustly healthy persons—still did not permit deliberate intrathoracic procedures to be done with any expectation of success. Two papers that appeared consecutively in the same journal in 1904 proposed opposite approaches to respiratory support in the presence of surgical pneumothorax, by means of differential pressure chambers. Both methods were reasonably successful in clinical use. The life span of the static-pressure chambers was brief, however, and within a few years they were being superseded by cyclic positive-pressure inflation via the airway. The opposing methods are remembered under their German names, Unterdruck and Überdruck.

(Ann Thorac Surg 1989;47:933–8)

In the opening years of the twentieth century, thoracic surgery did not exist; not at least in the sense that a patient's pleural cavity could be opened widely under general anesthesia, in the absence of diffuse pleural adhesions, and the patient be expected to survive for more than a few minutes. Surgical anesthesia had been introduced more than 50 years before, and antisepsis had long since given way to asepsis in the operating room, but to open the chest still meant instant death, with only unpredictable exceptions.

Simultaneous but Opposing Insights

In 1904 two papers appeared consecutively in a German periodical entitled *Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie*, or translated literally, "Communications From the Frontier-Districts of Medicine and Surgery" [1, 2]. Eighty-four and 18 pages in length, the papers described opposite approaches to the problem of open pneumothorax under general anesthesia, thus marking the birth of what was to become thoracic surgery.

The editors of *Mitteilungen* were a physician and a surgeon, the latter Johann von Mikulicz, professor of surgery and director of the University Surgical Clinic at Breslau. Mikulicz's name is remembered in connection with two-stage resection of the colon, seldom used today, and in the eponym for the familiar pyloroplasty. He wished most of all to develop a technique for transpleural resection of the esophagus, the results of which had been disastrous in both animals and patients. In October 1903 he had assigned one of his young surgical trainees, Dr Ferdinand Sauerbruch (Fig 1), to work on the problem.

Sauerbruch had received his medical degree at Leipzig in 1902, at the age of 27, and had completed 1 year of surgical training under Mikulicz. He immediately devoted all his energy to the problem, and earlier in 1904 had already published a discussion of the subject with some preliminary findings in another journal [3].

> In October of this last year Herr Geheimrat von Mikulicz suggested that I conduct an experimental study of possible methods by which the harmful effects of pneumothorax could be eliminated during intrathoracic operations. Principally, he [Mikulicz] had in mind transpleural resection of the esophagus, which until now has been associated with only the worst results both in animal experiments and in patients. The principal reason for such disastrous results was the pneumothorax which necessarily accompanies the operation, and

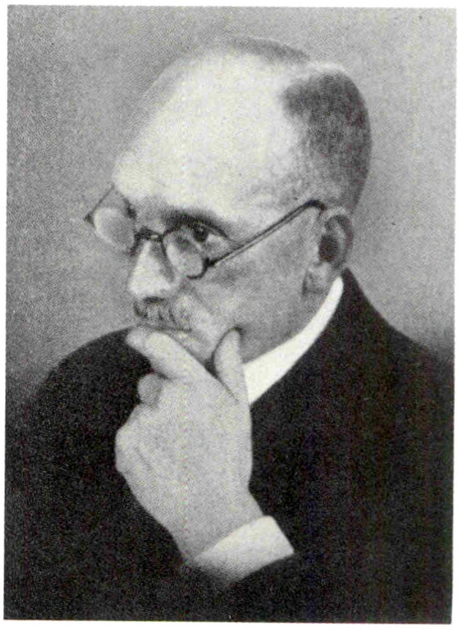

Fig 1. Ferdinand Sauerbruch (1875–1951), later in life. Originator of the negative-pressure chamber, the "Unterdruck" system. (Reprinted from Steele JD, ed, The surgical management of pulmonary tuberculosis, 1957. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

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Quotations from Drs Sauerbruch, Brauer, and von Mikulicz are in translation by Dr Meyer.

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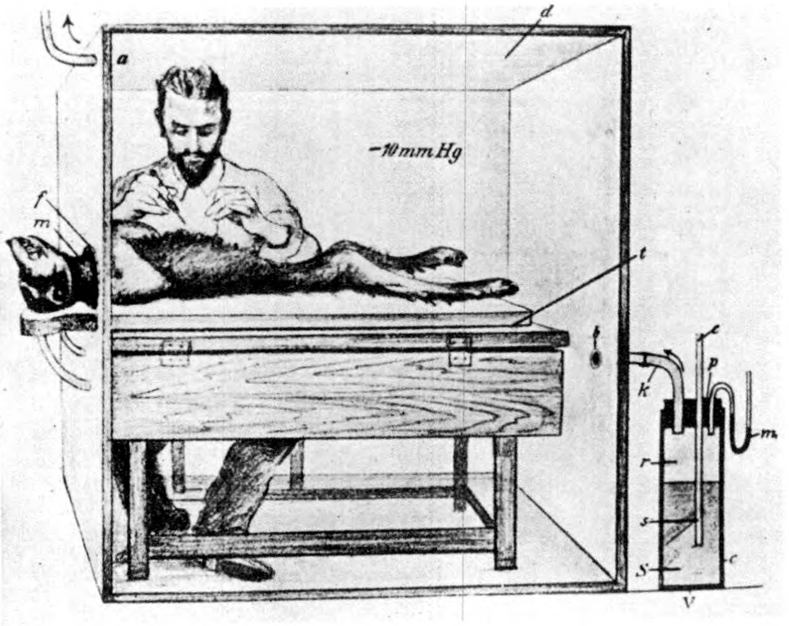

Fig 2. Sauerbruch's negative-pressure chamber designed for intrathoracic surgery on animals, 1904. A rubber collar (m) *seals the chamber at the animal's neck. (Reprinted from [1].)*

> the functional loss of the lung collapsed under atmospheric pressure. In the case of dogs, resection of the lower esophagus nearly always results in opening of both pleural cavities, so that the majority of the animals operated upon in this way die on the operating table. The physiologists have for a long time already assisted intrathoracic operations, such as vagotomy, by artificial rhythmic inflation of the collapsed lungs through a cannula tied airtight into the trachea by a separate procedure. During the previous year, Herr Geheimrat von Mikulicz had performed a series of esophageal resections in dogs by this method; the results however were not satisfactory, so that he considered the method to depend partly on chance. It was obvious that the harmful effects of atmospheric pressure had to be overcome in some other way, through the production of suitable negative pressure in a portion of the operating room, which would allow deliberate opening of the pleural cavity.
>
> Whether this method would prove feasible, and whether the desired results would follow, was from the first very questionable. So my task was to study the physiologic conditions involved, and to find the best method by which the technical problem could be overcome. As preparation, I first performed physiologic experiments upon rabbits and dogs, on the changes in blood pressure, the characteristics, and importance of respiratory movements with and without artificial ventilation, that is, inflation of the lungs with air after the manner of the physiologists. Review of the previous publications on this question showed, as far as I could see, insufficient studies of the ill effects of pneumothorax with and without artificial ventilation.

Inflation of the lungs with bellows, through a tracheal cannula, had been studied by Andreas Vesalius before 1555 [4], and had been demonstrated before the Royal Society by Robert Hooke in 1667 [5]. The method was able to maintain life, apparently indefinitely, while the chest cavity was open. Sauerbruch [3] mentions that the method was used commonly during physiological experiments. Why had it not been satisfactory for Mikulicz? First, there was the problem of a separate operation, and ligation of a cannula into the trachea. In addition, Sauerbruch intimates elsewhere that inflation of the lungs appeared to obstruct pulmonary blood flow, and presumably inflation pressures were not monitored. He appears to have been convinced that spontaneous respiratory movements were essential, so that respiratory rate would remain under the animal's own physiological control. He could see no way of accomplishing this except by maintaining negative intrapleural pressure, even though the pleural space was to be widely open.

> A change occurs when positive pressure enters the pleural cavity, that because of its own elasticity the lung collapses to a smaller volume. The higher the pressure within the pleura, the more equalization occurs with pressure inside the lung, and the greater becomes the effect of the lung's elasticity. Conversely, the lower the [pleural] pressure, the less the effect of elasticity. The inner pressure can actually overcome the lung's elasticity so that no collapse will occur. In other words: If we maintained the physiologic differential pressure during surgical opening of the chest, the lung would remain expanded; this much was self-evident. Furthermore, I hoped that by this method we could eliminate the dangers of pneumothorax, which are directly tied to collapse of the lung, and thus maintain the lung in its previously functional state, for the purpose of adequate gas exchange. . . We hoped greatly for *the possibility that one side of the chest could be opened without the harmful effects of pneumothorax, and without artificial ventilation.* [Emphasis in the original.]
>
> In order to determine experimentally the correctness of this hypothesis, I needed to accomplish opening of the pleural cavity while retaining the normal physiologic state of negative intrapleural pressure. To this end, I first constructed an exceedingly primitive apparatus. An open glass cylinder was closed off at both ends by sheets of rubberized cardboard. At one end three holes were made in the cardboard, two smaller and one larger; at the other end only one larger hole.
>
> The experimental animal was placed through the larger holes, so that its head protruded from one side, its lower body and hind limbs from the other, while its thorax and upper

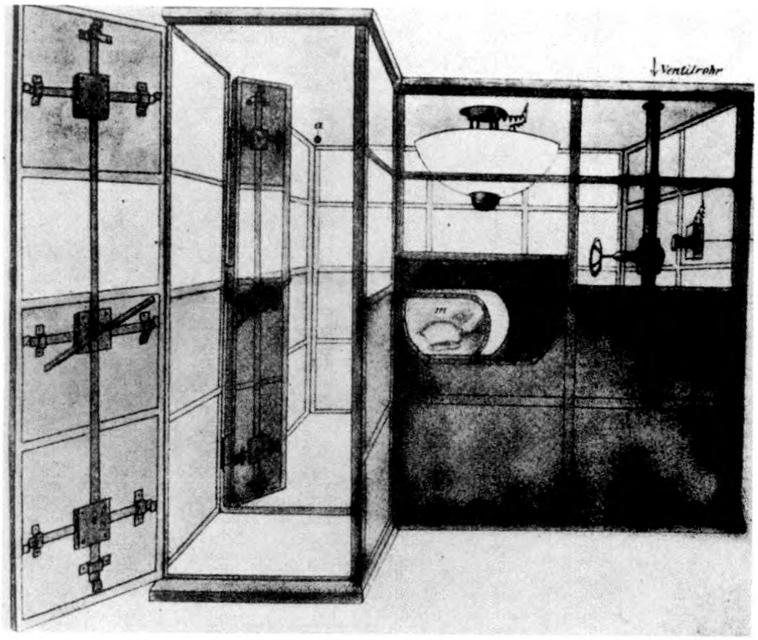

Fig 3. Large negative-pressure chamber built at the University Surgical Clinic in Breslau, 1904, for intrathoracic operations on patients. The object labeled m *in the center is the rubber cuff forming an air seal at the patient's neck; the patient's head protruded outside the chamber at this point. The air-lock cubicle opens at left. (Reprinted from [1].)*

> abdomen remained within the cylinder. After bringing together all the necessary instruments, I placed my hands into the smaller openings. Thereafter, all the openings were closed air-tight by rubber collars and glue, while an assistant connected a drainage tubing to the cylinder through which air was withdrawn until negative pressure developed, controlled by a mercury manometer at about the level of −10 mm. Now I opened the thorax; the lung did not collapse, and the animal's respirations continued undisturbed, without dyspnea. After about three minutes the occluding cardboard was accidentally torn in one spot; as a result the animal's lung collapsed, and after violent respiratory exertions the animal died [1].

A larger chamber for animal operations, enclosing the surgeon and his instruments as well as the animal's body up to the neck (Fig 2), convinced Sauerbruch that the method was feasible and that intrathoracic operations could be performed successfully. With Mikulicz's approval, he had a full-sized chamber constructed for clinical use.

> Since there has been great interest in the design of our large operating chamber, I will now give precise details of its construction and equipment. The pneumatic chamber [Fig 3] is a room with a volume of 14 cubic meters, constructed in the same manner as the above-mentioned wooden box. Floor, lower walls, and foundations are of heavy sheet iron. Above the height of 1.3 meters the wall is made of plate glass. The length of the chamber is 2.5 m, the width 2.25 m, the height 2.5 m. All connections between the iron plates are secured air-tight by welding. One side and the floor are completely solid, while on the other sides an iron frame begins at the height of 1.3 m, so constructed that each square opening is divided off and braced by iron rails. These iron rails are grooved to hold securely large plates of glass. The glass plates are 12 mm thick and can withstand a pressure difference of about 70 mm of mercury. In the beginning we had a great deal of trouble securing the glass plates air-tight in the grooves. We had used rubber inserts as seals and, in order to secure them, had to bend inward the iron beams from both sides; this could not be done easily and frequently broke the glass plates. Therefore we subsequently made the sealing with a mixture of putty and glue, and achieved a satisfactory airtight closure. The opening for the patient's head, located in the wide side of the chamber at a height of 92 cm, is oval in shape, 35 cm high and 50 cm long. A double rubber collar is secured within it, similar to the ones we had used for the animal experiments. On the corresponding outer side of the chamber is located an appropriate support for the patient's head. A large ceiling lamp, as shown in [Fig 3], is airtight but accessible from outside the roof of the chamber, and provides adequate illumination; moreover, within the chamber are 4 electric outlets, into which additional incandescent lamps can be connected. The valve for control of pressure consists of a copper cylinder 1 m in height and about 25 cm in diameter, containing water, which is open to the outside atmosphere through an iron pipe 12 cm in diameter. Control of the air pressure here does not depend on adjusting the exhaust pump, as in the first small chamber, but on the automatic functioning of this water valve.
>
> Evacuation of air is accomplished by a suction pump, which at top speed can evacuate 300 liters per minute; it is driven by a one-horsepower electric motor. The pump can serve as both oxygen and pressure pump, and is connected to the interior of the chamber through two valve systems. Valves, motor, and pump can all be regulated from the interior of the chamber. In case of malfunction of the machinery, a second, smaller, manually operated pump is available with a capacity of 100 liters per minute. The doorway to the chamber is located beside the head-portal, 75 cm in width, so that an operating table can be brought inside. In order to maintain isolation of the chamber during an operation, outside this door is a lock-cubicle about 53 cm long and 58 cm wide. This cubicle is closed off by a second air-tight door. The bolting of both doors onto rubber gaskets, by an 8-armed lever on the door frame, seals us within. This small cubicle is connected to the pumps separately from the main chamber, and adjusts precisely to

> the same pressure that exists in the main chamber . . . In 8 cases already this apparatus has performed flawlessly [1].

The Opposite Approach

The author of the second of the *Mitteilungen* papers [2] was Ludolph Brauer (Fig 4), 10 years older than Sauerbruch and already a professor of internal medicine at Heidelberg. The operating internist was a phenomenon of the time, at least in the area of chest disease and particularly tuberculosis. Having adopted methods of temporary collapse therapy, phthisiologists were eager to get on with methods of permanent collapse, and Brauer later was largely responsible for the introduction and standardization of thoracoplasty as definitive treatment. Because of simultaneous publication and the issue of priority, Mikulicz added an editorial footnote to Brauer's paper, giving him equal credit in generous terms [6].

> In my discussion, "Operations Within the Chest Cavity With the Aid of the Sauerbruch Chamber" in issues 15 and 16 of the German Medical Weekly [Deutsche medizinische Wochenschrift] of 1904, I made mention of the question of priority: whether the method of Herr Dr Sauerbruch could claim originality, or the positive-pressure system of Herr Professor Brauer, which is to say, the *inversion* of the Sauerbruch method. I gladly take this occasion to state, and to stress explicitly, that the explanations given us have cleared the matter beyond a doubt. The concept of the positive-pressure method occurred to Herr Professor Brauer entirely independently, and he pursued his investigations without having any knowledge of our researches in the same direction. There is no doubt, that if positive-pressure management proves to be useful not only in animal experiments but also in patients, it will mean an important technical simplification of the entire method.

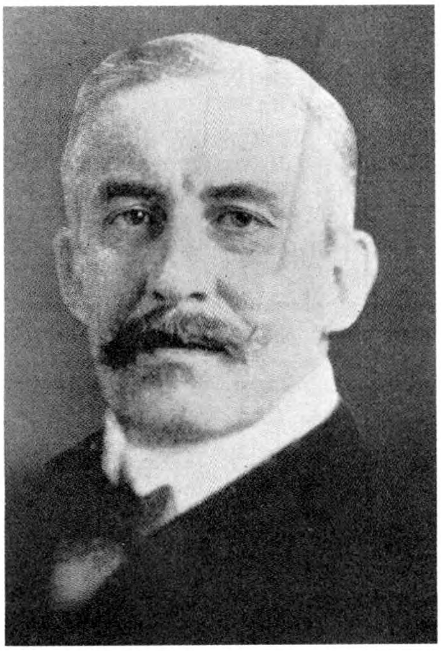

Fig 4. Ludolph Brauer (1865–1951), designer of the positive-pressure cabinet, the "Überdruck" system. (Reprinted from Steele JD, ed, The surgical management of pulmonary tuberculosis, 1957. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

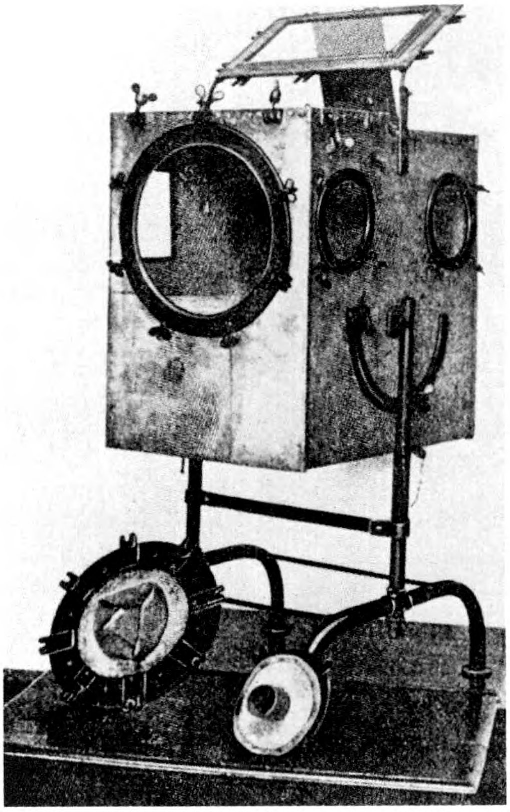

Fig 5. Brauer's positive-pressure cabinet designed for human patients, 1904. The two disc-shaped objects at bottom are (left) *the brass ring and rubber collar for sealing the chamber at the patient's neck, and* (right) *ring and rubber collar for sealing one of the smaller openings around the anesthetist's wrist. (Reprinted from [2].)*

Brauer pointed out that physiologists had also used constant intratracheal positive pressure as an aid during thoracotomy, again applied through an airtight tracheal cannula. To avoid surgical cannulation of the trachea and to apply the pressure by means of a chamber would have the same effect as the Sauerbruch method, and would be much less cumbersome.

> With the help of a chamber, a constant pressure difference between the inner and outer surfaces of the lung can be created, and the lungs can be maintained in the same expanded state in which they are normally held through the elasticity of the thoracic wall. Moreover, animals possess the faculty of self-regulation of the depth and rate of their own respirations.
>
> I believed that both these conditions could be fulfilled, if the constant pressure difference were achieved through the use of *intrabronchial positive pressure* [emphasis added].

> Figure [5] shows the design of a [positive-pressure] cabinet, which has a volume of about one-half cubic meter; this cabinet is designed . . . to isolate the patient's head by the application of a rubber collar; the patient's body however remains outside the chamber. The patient's anesthesia can be induced beforehand, and the collar first fitted onto the cabinet, when the danger of pneumothorax is thought to be imminent. To accomplish this, the collar is fastened to a brass ring, which can be quickly secured to the cabinet. Over the patient's face is an appropriately sized glass porthole which can be securely

> closed. This porthole would first be closed when one wishes to initiate the positive pressure. In this manner, it is possible to make all preparations and to conduct the operation, without causing the patient any difficulty at all. In the same way, the cabinet can once more be opened when the danger of pneumothorax is past.
>
> The control of anesthesia and maintenance of positive pressure—measures which must be considered together—can be done as follows. The necessary level of air pressure and an ample ventilation of the cabinet are provided through two valves. Through one of these valves is supplied the air pressure; the other functions as a vent, and regulates the air pressure within. The flow of air through the cabinet can be controlled as needed, so that the patient in the chamber not only receives adequate air for ventilation, but clean air free from anesthetic gases. The anesthetic vapors are brought in by another route. A modified Roth-Dräger chloroform apparatus prepares the anesthetic mixture in the desired proportions; the mixture is under slight pressure from the oxygen tank, and is brought through tubing into the cabinet and directly to the anesthetic mask [2].

At the time of writing, Brauer had conducted only animal experiments by his method, and Mikulicz's editorial footnote alluded to the fact that the method had not yet had clinical trial. But it was apparent to both that the positive-pressure system could represent a great simplification over the negative-pressure system.

> It is important to note, that since this simple apparatus has been improved in many ways and has been made safe and practical, it can make possible for everyone the performance of surgical operations according to Sauerbruch's principles. This apparatus does not need to remain fixed in place, as does the large chamber. Whether such a box can entirely replace the large chamber, only additional practical experience will decide; but for many operations the box [positive-pressure cabinet] will doubtless prove to be adequate. Therefore it is likely to be valuable in many circumstances, since it is very easy to transport; and it may be useful in war-time surgery for the treatment of chest and heart wounds [2].

The two systems have been spoken of, in these papers and ever since, as *Unterdruck* (literally, under-pressure) and *Überdruck* or "over-pressure." Positive-pressure and negative-pressure systems would be a more familiar terminology, but the German names identify the two methods in their historical context.

Epilogue

Dr Willy Meyer of New York, later the founder of the American Association for Thoracic Surgery, maintained close contacts with German surgery. Born in Germany and a medical graduate of Bonn University, he had received his surgical training under Friedrich Trendelenburg at Leipzig, then emigrated to the United States in 1884 and began his practice in New York City. Already older than either Sauerbruch or Brauer, he was deeply interested in their work. He had a chamber built that incorporated both high-pressure and low-pressure systems at the German Hospital of New York, now Lenox Hill Hospital [7]. Samuel Robinson of Boston had an improved high-pressure cabinet built at the Massachusetts General Hospital [8], as did Hugh Morriston Davies at the University College Hospital in London [9]. Davies's apparatus supported the patient's respiration through the first planned lobectomy for lung cancer. But the lifetime of the constant-pressure chambers was relatively short; Willy Meyer and others noted cases in which patients tolerated the anesthetic and the operation poorly, and attributed these bad results to inadequate ventilatory exchange with consequent CO_2 retention [10]. In 1909 Henry H. Janeway and Nathan Green [11] described a cabinet similar to Brauer's that applied intermittent cyclic positive pressure, with the result that the patient's own respiratory movements often were abolished, achieving what we now call controlled respiration. In the same year, Samuel J. Meltzer and John Auer [12] described continuous insufflation of the lungs by a foot pump, recommending peroral intubation of the trachea as the best way to manage the airway. Peroral intubation had been known since 1880 [13] but had been regarded as too difficult for routine use. Meltzer, though a physiologist, later served as first president of the American Association for Thoracic Surgery. In the following year, 1910, a cuffed endotracheal tube indistinguishable in design from that of today was described by George Dorrance of Philadelphia [14]. Thereafter, intermittent positive-pressure inflation of the lungs gradually came to dominate the other forms of respiratory support under anesthesia.

Within a year after publication of the two *Mitteilungen* papers, Professor von Mikulicz died of carcinoma of the stomach, at the age of only 55. The German province of Silesia was incorporated into Poland after World War II, and the city of Breslau renamed Wroclaw. The building that housed Mikulicz's University Surgical Clinic still stands [15]. Brauer became professor and director of medicine at Marburg, and later at Hamburg. Sauerbruch held several chairs of surgery, finally becoming professor at the University of Berlin in 1927. As such, he was the foremost surgeon of the Third Reich through the end of World War II, as William L. Shirer has noted [16]. Both Sauerbruch and Brauer died in 1951. Several surgical instruments of Sauerbruch's design remain available from manufacturers in the United States, notably the massive Sauerbruch rongeur (Pilling, division of Narco Scientific, Fort Washington, PA) and the Sauerbruch rib shears (Codman and Shurtleff, Inc, Randolph, MA).

The principle of the low-pressure Sauerbruch chamber, together with the cyclic pressure change of Janeway and Green, were revived by Drinker and Shaw [17] in the design of a practical mechanical respirator, the famous "iron lung" of the polio era. The Drinker-Shaw respirator probably was the last appearance of the Unterdruck principle, though it no longer made use of static negative pressure.

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Free Radicals and Myocardial Protection: A Surgical Viewpoint

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Oxygen-derived free radicals are now considered important contributors to tissue injury associated with ischemia and reperfusion. Transition metals, primarily iron, greatly enhance the generation of these active species, which can destroy a large variety of biomolecules, in particular the lipid components of cell membranes. This review tries to demonstrate why cardiopulmonary bypass and aortic cross-clamping are situations that predispose to oxygen free radical production, and how "anti-free radical" agents such as enzymatic scavengers, antioxidants, and iron chelators may prove to be useful therapeutic adjuncts in the clinical setting of open heart surgery.

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There is little question that the improvements in techniques of myocardial protection that have been accomplished over the past years have contributed to reduced operative mortality and morbidity of cardiac-related origin. However, changing patterns of surgical indications have concomitantly elicited new subsets of high-risk patients, such as those undergoing redo operations or emergent revascularization procedures after failure of percutaneous transluminal coronary angioplasty. In such patients, the frequent deterioration of preoperative hemodynamics caused by impaired left ventricular function or evolving myocardial ischemia makes intraoperative cardiac preservation a still more critical determinant of the postoperative outcome.

In this context, a great deal of interest is currently paid to oxygen free radicals because of the growing experimental evidence that these reactive species might be involved in the pathogenesis of myocardial tissue injury associated with ischemia and reperfusion [1–4]. The relevance of this concept to cardiac surgery is due to the fact that during open heart procedures, the conditions of both ischemia and reperfusion are under the surgeon's control. This raises the possibility that free radical injury could be effectively acted on by appropriate interventions implemented before, during, or after the period of aortic cross-clamping.

However, the relative novelty of the concept of free radical injury in the surgical setting, the tediousness of the terminology used for describing free radical–related events, and the conflicting results yielded by the experimental evaluation of some free radical scavengers are all factors that can make surgeons somewhat skeptical and lead them to assume that this aspect of myocardial preservation still has more to do with basic chemistry than with clinical practice. This review tries to demonstrate that such an assumption is probably erroneous.

Background Data

Definitions

A free radical is a molecule that has an odd number of electrons. Because it tries to pair this odd electron, such a molecule is, in general, a chemically reactive species. When a free radical ($R^{\cdot}$) reacts with a stable compound (BC), that is, a compound that has an even number of electrons, one of the products of the reaction will automatically have an unpaired electron ($C^{\cdot}$) and, in turn, will behave as a free radical:

$$R^{\cdot} + BC \longrightarrow RB + C^{\cdot}.$$

This propagation sequence of radical-generating reactions has critical consequences in vivo, where one of the elective targets of free radicals is the lipid component of cell membranes [5]. Typically, a free radical will attack unsaturated fatty acid side chains (Lipid-H) by abstracting an atom of hydrogen and leaving a carbon-centered lipid radical ($\text{Lipid}^{\cdot}$):

$$R^{\cdot} + \text{Lipid-H} \longrightarrow RH + \text{Lipid}^{\cdot}.$$

In the presence of oxygen, this lipid radical gives rise to a peroxy radical ($\text{Lipid OO}^{\cdot}$):

$$\text{Lipid}^{\cdot} + O_2 \longrightarrow \text{Lipid OO}^{\cdot}.$$

The peroxy radical can then remove a hydrogen atom from additional fatty acid side chains and thereby propagate the sequence by producing another lipid radical along with a lipid peroxide (Lipid-OOH):

$$\text{Lipid OO}^{\cdot} + \text{Lipid-H} \longrightarrow \text{Lipid-OOH} + \text{Lipid}^{\cdot}.$$

These lipid peroxides are, in turn, able to decompose in the presence of transition metals such as iron (the role of iron will be discussed in a later section) to give additional unstable intermediates (such as the previously mentioned peroxy radicals), which further contribute to the loss of membrane integrity, subsequent disturbance of ionic fluxes, and, ultimately, cell damage [3, 5]. This scheme of

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events accounts for the possibility of using the assay of lipid peroxidation products as a means of assessing free radical–mediated tissue injury [1].

In addition, free radicals can cause denaturation of proteins, in particular through oxidation* of their thiol (-SH) residues [6]. This observation provides a basis for the putative protection afforded by exogenously supplied "donors" of thiol residues such as reduced glutathione (GSH).

Free Radicals Under Physiological Conditions

Under physiological conditions, 95% of oxygen is transformed into water by the mitochondrial cytochrome oxidase complex [2–5]. This transformation involves what is usually referred to as a tetravalent reduction; in simpler terms, this means that there is a simultaneous gain of four electrons by molecular oxygen without the production of any intermediate.

We are thus left with 5% of residual oxygen, which is diverted toward a univalent reduction pathway. The major characteristic of this pathway is that molecular oxygen gains electrons in a sequential fashion, each gain leading to the generation of a reactive intermediate, which is a free radical. With the acceptance of the first electron, the superoxide anion ($O_2^{\cdot -}$) is formed:

$$O_2 \xrightarrow{e^-} O_2^{\cdot -}.$$

The gain of a second electron gives rise to hydrogen peroxide (H_2O_2):

$$O_2^{\cdot -} \xrightarrow{e^- + 2H^+} H_2O_2.$$

The gain of a third electron gives rise to the hydroxyl radical (${}^{\cdot}OH$):

$$H_2O_2 \xrightarrow[H_2O]{e^- + H^+} {}^{\cdot}OH.$$

This hydroxyl radical is usually considered one of the most cytotoxic free radicals because of its strong oxidizing properties, which can affect almost all kinds of biomolecules.

These free radicals are produced in limited amounts under normal conditions. They are prevented from exerting their harmful effects by naturally present intracellular defense systems, which permanently inactivate them. These defense mechanisms consist primarily of enzymatic scavengers. Thus, superoxide dismutase (SOD) catalyzes dismutation of superoxide anion to hydrogen peroxide while two additional enzymes, catalase and glutathione peroxidase, degrade hydrogen peroxide to water and oxygen, thereby bypassing the hydroxyl radical generation step. Other intracellular defense mechanisms against free radicals include low molecular weight antioxidants such as vitamin E or GSH, which, by virtue of its thiol residue, is highly effective in trapping unpaired electrons.

The Role of Iron

We have mentioned that the hydroxyl radical is a particularly reactive oxidizing species that can cause extensive tissue destruction. Because there are no physiological defense systems that can scavenge excessive quantities of hydroxyl radical, it is critically important to prevent the generation of this radical. Hydroxyl radical (${}^{\cdot}OH$) generation actually results from a reaction between the one-electron reduced product superoxide anion ($O_2^{\cdot -}$) and the two-electron reduced product hydrogen peroxide (H_2O_2):

$$O_2^{\cdot -} + H_2O_2 \longrightarrow O_2 + OH^- + {}^{\cdot}OH$$

This reaction, which is referred to as the Haber-Weiss reaction, requires the participation of a transition metal catalyst, usually iron [7, 8].

As already stated, iron is also involved in the chain reaction of lipid peroxidation because transition metals catalyze the decomposition of lipid peroxides into unstable intermediates, which contribute to disruption of cell membranes.

Again, these apparently basic considerations may be relevant to cardiac surgical practice because of the availability for human use of well-characterized iron-chelating drugs such as deferoxamine.

Free Radicals During Ischemia and Reperfusion

During ischemia, the lack of oxygen activates various sources of free radicals, in particular some sites of the mitochondrial electron transport system and the arachidonic acid pathway [3, 9]. It is here appropriate to recall that the concentration of xanthine oxidase, an enzyme that is considered a potential source of superoxide radicals through oxidation of hypoxanthine [10], is highly species dependent and, in particular, is minimal in rabbit and human myocardium [11]. This suggests that the still controversial "antiischemic" effects of the drug allopurinol [12, 13] could be predominantly related to the ability of this compound to scavenge hydroxyl radicals [14] rather than to the commonly alleged mechanism of xanthine oxidase inhibition.

Free radical–generating reactions can proceed at extremely low oxygen tensions [9], which are actually expected to be present in ischemic myocardium whether oxygen is derived from autooxidation of catecholamines [15] or supplied through collateral blood flow. Thus, it is likely that free radical production starts during the ischemic period, as demonstrated by experimental [16] and clinical [17] studies that have reported that lipid peroxidation products increase while coronary flow is still interrupted. On the other hand, ischemia is associated with a depletion of the tissue content of antioxidants, including SOD, catalase, peroxidase, and GSH [18–22].

Because free radical production is largely dependent on oxygen tension [23], it is not unexpected that this phenomenon occurs to a much greater extent during reperfusion, when reactive hyperemia supplies abundant amounts of oxygen to previously "primed" sources of free radicals, than during ischemia. Restoration of coronary blood flow also brings an additional source of free radicals consisting of activated polymorphonuclear leukocytes (PMNs) [24]. This burst of free radical production overwhelms the scavenging capacity of the reduced cellular defense mechanisms. As a result of this imbalance, free radical–mediated deleterious effects are unopposed, thus accounting for loss of normal mitochondrial and sarcoplasmic reticulum function [3], disturbed membrane permeability, and disruption of cellular transport processes [5, 18], all of which are salient features of the so-called reperfusion injury [25].

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* An oxidation corresponds to a gain of oxygen or to a loss of a proton or an electron. A reduction corresponds to a gain of a proton or an electron or to a loss of oxygen. An oxidant is an acceptor of electrons, whereas a reductor is a donor of electrons.

Are Free Radicals Produced During Open Heart Operations in Humans?

From a theoretical standpoint, there are at least two mechanisms that can result in free radical production during open heart procedures in humans. First, it is well established that cardiopulmonary bypass per se results in a complement-mediated activation of PMNs [26–28]. This "activation" corresponds, among other events, to a production of oxygen free radicals, in particular superoxide anions and hydrogen peroxide [24]. In addition, these activated PMNs release lactoferrin, a protein that stores iron, into the extracellular environment [28]. It has been reported that superoxide anion could mobilize lactoferrin-bound iron [28], thus making "free" iron available for catalyzing the hydroxyl radical–generating Haber-Weiss reaction. This scheme of events is likely to proceed in a self-propagating manner because PMN–derived free radicals can trigger the secretion by membrane phospholipids of chemotactic substances, that is, substances that cause a further recruitment of activated PMNs, which, in turn, will produce additional free radicals [29].

Second, most cardiac operations now involve a transient period of aortic cross-clamping. From the preceding data, it is not unexpected that this ischemia/reperfusion sequence results in production of free radicals in myocardial tissue [30]. Such a phenomenon is also likely to occur during heart transplantation when the ischemically stored donor heart is abruptly reoxygenated by the recipient's blood.

From a practical standpoint, the difficulty in assessing whether these mechanisms are truly operative in the clinical setting stems from our inability to measure free radicals directly by simple and reliable techniques. For this reason, a great deal of interest should be paid to the clinical study of Cavarocchi and co-workers [31]. To the best of our knowledge, it is the first to provide more direct evidence of free radical generation during cardiopulmonary bypass in humans by demonstrating elevated levels of hydrogen peroxide at the end of the procedure. In keeping with these findings, Royston and associates [32] reported an increase in lipid peroxidation products after cross-clamp removal in patients undergoing myocardial revascularization; this lends additional support to the theory implicating free radicals in organ injury associated with cardiopulmonary bypass. More specifically, in this study, the fact that a significant release of peroxidation products occurred at the same time as pulmonary neutrophil sequestration strongly suggests that PMN–derived oxidant species could be critical mediators of the lung injury syndrome after bypass [33].

How Can Free Radical Injury Be Counteracted?

Nature of Compounds

For practical reasons, we divided compounds expected to reduce free radical–mediated tissue injury into three categories: enzymatic scavengers, low molecular weight antioxidants, and metal chelators.

ENZYMATIC SCAVENGERS. Among enzymatic scavengers, the most extensively studied compound has been SOD. In experimental models of myocardial global ischemia, the use of SOD has usually yielded positive results, that is, in most studies, SOD–treated hearts have demonstrated a better postischemic recovery than controls. It is noteworthy that this improved protection has been reported regardless of whether the enzyme was given before [34] or during [35–38] the ischemic episode and whether the experimental preparation was a buffer-perfused isolated heart model [35, 38], a blood-perfused isolated heart model [36], or an in vivo animal model of cardioplegic arrest [34, 37]. Similarly good results have been obtained in experimental models of heart transplantation [13, 39]. It is also noteworthy that the effects of SOD do not seem to be mediated by hemodynamic changes that might favorably affect myocardial oxygen consumption and thus more likely reflect a direct cytoprotective action.

These results contrast with those obtained in models of regional ischemia, in which some studies [40, 41] have reported a reduction in myocardial infarct size in SOD–treated animals whereas others [42, 43] failed to document any beneficial effect of enzyme treatment. It is possible that the greater number of experimental variables involved in regionally ischemic preparations, as opposed to preparations of global ischemia, accounts for the conflicting results obtained in the former setting [44].

Regardless of the experimental conditions, we believe it is important to emphasize that SOD may not be the ideal scavenger, at least when it is used alone. The reason is twofold. First, there is experimental evidence that acidosis, which occurs to some extent during global ischemia, shifts the predominant radical species from superoxide anion (the substrate for SOD) to hydrogen peroxide [45]. This increased rate of spontaneous dismutation of superoxide anions would lessen the relative importance of enzymatic dismutation and therefore make the use of SOD redundant in this setting.

Second, even if one assumes that SOD is operative on superoxide radicals still generated during global ischemia, the net result of its action will be an increased accumulation of hydrogen peroxide, the major danger of which is the iron-catalyzed production of highly cytotoxic hydroxyl radicals. These considerations may explain why some studies have shown SOD to be less effective than enzymes like catalase [12, 46] or peroxidase [38, 47], which are targeted at inactivating hydrogen peroxide. An additional advantage of peroxidase is that it can also scavenge lipid peroxides and hence interrupt the chain reaction of lipid peroxidation. In summary, the lack of additional protection after SOD treatment reported in some studies must not lead to the misleading conclusion that free radical scavenging is an erroneous concept, as hydrogen peroxide, rather than superoxide anion, might be the elective oxygen species on which to act.

A last issue to be addressed when dealing with these enzymes, whether SOD, catalase, or peroxidase, is their site of action. For a while, their true protective action has been questioned in view of their high molecular weight, which makes their intracellular penetration unlikely. It is now possible to reconcile the alleged efficacy of these enzymes and their anticipated inability to cross cell membranes, because it has been shown that free radicals could be present extracellularly [48], whether they are "extruded" from intracellular sources or released in situ, in particular from activated PMNs. Thus, while remaining probably ineffective on intracellular oxygen free radicals, intravascularly administered enzymatic scavengers could at least exert their protective effects at the endothelial level [49].

LOW MOLECULAR WEIGHT ANTIOXIDANTS. Among the various compounds such as vitamin E or coenzyme Q that have been investigated, GSH is probably the most important antioxidant to be considered in this category. Experimentally, GSH has been shown to improve recovery after ischemia when given as an additive to the cardioplegic solution [38] or to the initial reperfusate [50]. These protective effects are most likely due to the thiol residue present on the reduced form of the molecule, as thiol residues are extremely effective in trapping unpaired electrons according to the following scheme:

$$\text{G-SH} + e^{\cdot} \longrightarrow \text{GSH}^{\cdot};$$

$$\text{GSH}^{\cdot} + \text{GSH}^{\cdot} \longrightarrow \text{GSSG} + H_2,$$

where GSSG = oxidized glutathione.

Myocardial ischemia results in a depletion of the tissue content of GSH [22] and protein-bound thiol residues [6], which correlates with an increased lipid peroxidation [51]. Thus, one might expect exogenously supplied GSH to compensate, at least partly, for this loss of endogenous stores, therefore improving the capacity of ischemic and reperfused myocardium to handle oxidative injury [52].

These observations have practical implications. Drugs that enhance glutathione synthesis are clinically available, and although their primary indication has been the treatment of certain hepatic diseases [52], it might be worthwhile to reconsider their potential usefulness for limiting heart reperfusion injury.

METAL CHELATORS. As previously stated, transition metals, in particular iron, catalyze both the generation of the highly destructive hydroxyl radical and the reactions of lipid peroxidation [7, 8]. Thus, whereas the usual therapeutic approach to oxidative injury is the use of scavengers designed to inactivate free radicals, an alternative strategy consists of reducing the rate of production of radical species by chelating the metal catalysts involved in this production.

We think such an approach may have at least two important advantages. First, metal chelators are expected to have a broader spectrum of action than scavengers because they intervene at the common denominator of all oxidative mechanisms, namely, metal catalysis [8]. Second, some of these chelators exist as clinically available drugs that are well characterized in terms of toxicology, dose–effect relationships, and pharmacokinetics. Such is the case for the iron chelator deferoxamine. In vitro, this drug has been shown to inhibit lipid peroxidation [7], and it is tempting to relate this observation to the ability of deferoxamine to reduce the deleterious consequences of ischemia and reperfusion involving heart [12, 46, 53–55], lung [56], and brain [8] tissue. Clinically, our preliminary results with the use of low-dose deferoxamine in cardiac surgical patients have been encouraging [57] and lend additional support to the concept that iron chelation could be an effective means of improving cardioplegic protection.

General Conditions of Efficacy

TIMING OF ADMINISTRATION. From the large experimental data base now available, it is apparent that the prerequisite for free radical scavengers or metal chelators to be fully effective is that these compounds be supplied to the target tissue before the onset of reoxygenation [58, 59]. In cardiac procedures, if we assume that free radical production can start early after interruption of coronary blood flow, it appears even more logical to give "anti-free radical" agents at the onset of the ischemic period as additives to the initial cardioplegia infusion and, in particular for those who use the secondary cardioplegia (or "hot shot") approach [60], to provide an additional delivery of antioxidant compounds along with the last cardioplegia infusion immediately preceding release of the aortic cross-clamp. Furthermore, it should be remembered that complement activation can result in a release of free radicals, in particular from activated PMNs, very shortly after cardiopulmonary bypass has been initiated [26, 27]. This provides a rationale for implementing scavenging interventions in the immediate period before bypass [34, 47] with the hope of "loading" tissues with an amount of antioxidant agents sufficient to cope with the bulk of free radicals expected to result from the forthcoming periods of extracorporeal circulation and myocardial ischemia and reperfusion. Using the iron chelator deferoxamine during open heart procedures, we [57] have demonstrated both the feasibility and the efficacy of such a prophylactic treatment protocol. In the setting of heart or heart-lung transplantation, the addition of free radical scavengers to the storage solution has also been considered but might be less effective than the administration of these compounds at the time of reoxygenation of the donor heart by the recipient's blood [39].

TEMPERATURE. Because hypothermia is a major component of cardioplegic protection, one can question whether free radical–generating processes are still operative at low temperatures. The validity of this concern is reinforced by the fact that several experimental studies examining the ability of free radical scavengers to enhance cardioplegic protection have actually been performed under moderately hypothermic conditions.

In fact, maintenance of hypothermia during the period of global ischemia does not exclude a pathogenetic role for oxygen free radicals and hence the potential therapeutic usefulness of their scavengers. Even if one assumes that, as with all biochemical processes, the rate of free radical production as well as the rate of interaction between free radicals and scavengers is slowed in cold myocardial tissue, both of these processes are expected to become maximally operative as the heart is being rewarmed, that is, during the final phase of ischemic arrest. It is also reasonable to speculate that the tissue-damaging shift of the oxidation–reduction state of the cells toward oxidation will increase further when ischemic myocardium is being reperfused with normothermic (or almost normothermic) fully oxygenated blood at the time of release of the aortic cross-clamp.

These considerations probably account for the consistent ability of free radical scavengers to improve myocardial recovery after ischemia, even when cardioplegic arrest is conducted at 10° to 18°C [37, 38, 47, 53]. Thus, although these data strongly suggest that hypothermia per se does not invalidate the concept of free radical scavenging in the setting of surgically induced cold ischemic arrest, they also reemphasize that, regardless of the precise time at which free radical scavengers exert their protective effects, the end point remains that these compounds are present in ischemic tissue by the time the aortic cross-clamp is removed. The same conclusions hold true for iron chelators, as our group [53] has shown that administration of deferoxamine under conditions of cold (15° to 18°C) cardioplegic arrest did not preclude markedly improved postischemic mechanical recovery.

How Can We Assess the Efficacy of Anti-free Radical Interventions?

It is fair to acknowledge that this critical issue remains unsettled. Because the chemical reactions involving free radicals have extremely short kinetics (10^{-4} seconds), we currently lack a simple and reliable technique that would permit a direct identification of these species. In fact, most of the information on the implication of free radicals in tissue injury has been indirectly derived from the protective effect of an exogenous supply of their scavengers.

Nevertheless, techniques designed to provide a more direct visualization of oxygen free radicals do exist and include electron spin resonance and spin-trapping. The principle of electron spin resonance is to obtain a signal from a free radical and to convert this signal into a spectrum expected to be characteristic for this radical species [30]. The tissue containing free radicals, for example, an isolated heart subjected to ischemia and reperfusion, is placed in a magnetic field, and the unpaired electrons of free radicals are then excited under appropriate conditions. This excitation causes the unpaired electron to "jump" from its resting energy level to a higher energy level; this transition is converted into a spectrum, the characteristics of which should be specific for the free radical "housing" the excited unpaired electron.

The spin-trapping technique consists of perfusing the organ under investigation with certain chemicals (spin-trapping agents) that have the capability of reacting with free radicals and forming stable compounds with them [61]. Because of its binding on a stable carrier, the "trapped" free radical has a longer half-life, which makes easier its subsequent identification by electron spin resonance.

Although these techniques have yielded promising results, they must be investigated further. A critical issue is the true specificity of the recorded electron spin resonance spectra, and there is general agreement that the spectroscopic patterns of "excited" free radicals should be better characterized before a given spectrum can be readily attributed to a given radical species. In addition, in their present state, these methods can be applied only to biopsy samples or, at best, to isolated organs, which precludes their application in the clinical setting. Another limitation to their clinical use is related to the high toxicity of currently available spin-trapping agents.

Therefore, we are obliged to rely on only indirect criteria to assess the effects of anti-free radical interventions. Because free radical injury involves the lipid components of cell membranes, one of the most meaningful of these criteria is probably the measurement of lipid peroxidation products, either in biopsy samples of myocardial tissue or in the coronary sinus blood effluent. Until now, the assay of malonedialdehyde has been the most frequently used index of lipid peroxidation. This compound is an end product of the cyclooxygenase pathway of arachidonate metabolism. For this reason, there is currently general agreement that it lacks specificity [1, 4, 16].

The measurement of conjugated dienes is probably much more reliable [16]. The term *conjugated dienes* refers to carbon-centered lipid radicals after they have undergone a molecular rearrangement that tends to stabilize them (it is thus a sort of transition state between lipid radicals and peroxy radicals). In fact, conjugated dienes have been shown to increase drastically during cardioplegic arrest and postischemic reperfusion in humans [17], but the complexity of this assay technique presently restricts its widespread clinical use.

Another approach consists of quantifying the production of superoxide radicals generated by PMNs that have been harvested from the patient's blood at various stages of the surgical procedure and subsequently stimulated in vitro by appropriate substances that trigger the oxidative metabolism of these cells [29, 62, 63]. The responsiveness of PMNs to such a stimulation may provide information on the extent to which circulating PMNs have been activated, in particular by free radicals, in vivo. Using this technique, we [57] have shown that the production of leukocyte-derived superoxide radicals after bypass was twofold lower in deferoxamine-treated patients than in control patients. Additional studies are warranted to better define the clinical relevance of these findings.

Conclusion

It is clear that intraoperative myocardial protection has attained a level of efficacy that makes further improvement difficult to demonstrate. That such improvements are mandatory is nevertheless evident from the observation that open heart procedures in high-risk patients still carry a substantial cardiac-related mortality and morbidity. It would certainly be naive to consider that oxygen free radicals or transition metals involved in their generation are the only mediators of tissue injury incurred by ischemic and reperfused myocardium and, therefore, that the use of free radical scavengers or metal chelators will cause a dramatic improvement in the postoperative outcome for our patients. It is much more likely that progress in this field will result from a cumulative addition of minor changes involving preoperative management, surgical technique, formulation of cardioplegic solutions, maintenance of adequate myocardial cooling, manipulation of the initial reperfusate, and pharmacological or mechanical supportive procedures after bypass. It is only in the setting of such a multifactorial approach that limitation of free radical–mediated tissue damage may prove to be conceptually worthwhile and clinically helpful.

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The Society of Thoracic Surgeons Ad Hoc Committee on AIDS Report to the Membership

The Society of Thoracic Surgeons Committee on AIDS makes the following recommendations to thoracic surgeons:

1. Make every attempt to identify, prior to major elective surgery, patients who are positive for infection with the Human Immunodeficiency Virus (HIV) by voluntary testing. In so doing, be careful to comply with any applicable confidentiality statutes and/or informed consent statutes.
2. Use universal precautions against exposure to blood and other body fluids in the operating room and throughout the hospital, regardless of whether the status of the HIV serology is known.
3. Take a leadership role to encourage easing the current restrictions on HIV testing in order that we may learn more about: a) the risks of transmission of HIV, b) the role that a positive HIV status may play in affecting the results of treatment of other disease processes, and c) the possibility that surgery may accelerate the development of AIDS in the HIV positive patient.
4. Encourage hospital laboratories to develop the capability of providing rapid screening of patients for HIV.

Acquired Immunodeficiency Syndrome and the Thoracic Surgeon

Rarely in the course of history has a disease provoked such an emotional response as has the present epidemic of acquired immunodeficiency syndrome (AIDS). Because of the groups that are commonly affected, social stigmata are attached. Patients suffering from the disease have been socially outcast and denied employment, and in some cases have had difficulty receiving appropriate medical care. Legislators have felt it necessary to enact laws to protect the rights and dignity of these individuals. These laws can, at times, produce difficulties in the medical decision-making process because the physician cannot order an HIV serology as he or she normally orders other tests for patients. In California, for example, the physician must obtain specific, informed consent from the patient before performing the HIV test.

Physicians are deeply involved in this complex issue. Most of them have responded in the time-honored fashion of providing appropriate care for the individual patients. A few others have publicly expressed their fears of the potential risk for the members of the health care teams. Some have proposed mandatory serologic testing of all patients before performing certain operations. This risks producing a double standard of care, which might arouse cries of bias.

As the AIDS epidemic has evolved and patterns of transmission are better understood, emotional overtones should no longer play a role in the decision-making process. This report will attempt to outline the specific problems of the thoracic surgeon as related to AIDS and to suggest guidelines.

There are six distinct areas of special concern for the thoracic surgeon: (1) the risk of transmission of the disease from a patient to the surgeon and other members of the health care team, (2) the problems that would be produced by routine HIV testing of all patients and the resulting problems of protecting the confidentiality of those being tested, (3) the ethics and moral dilemma of refusing to care for these patients on the basis of the fear evoked by this risk, (4) the possibility that certain forms of treatment, such as the use of cardiopulmonary bypass equipment, may actually exacerbate the disease process by further immunosuppression, (5) the possibility that the response to cardiopulmonary bypass and the results of cardiac operations may be adversely affected by the presence of HIV infection, and (6) the medical-legal risk of HIV transmission to a patient through the use of blood products in surgical procedures.

Risk of Transmission of the Human Immunodeficiency Virus

The modes of transmission of the virus from one person to another have been established with a high degree of confidence. The presence of the virus has been established in virtually all body fluids: semen, vaginal secretions, blood, urine, saliva, cerebrospinal fluid, mother's milk, and almost certainly feces. It is not readily transmitted from one individual to another. Almost all transmissions are attributed to sexual acts (either homosexual or heterosexual), direct blood transmission as a result of needle sharing among drug abusers or blood transfusions from infected donors, or mother-to-offspring transmission during the course of pregnancy and the birth process. There have been a few instances of conversion of medical health care workers to a positive HIV status in which none of these specific risk factors applied. There also have been instances in which health care workers, known to be serum HIV negative, have converted to HIV positive after a specific exposure to HIV–positive blood either by needle stick, inadvertent injection, or splashing.

It should provide some reassurance to realize that casual contact with a patient with AIDS has not yet been reported to transmit HIV infection, even when family members are associated in close quarters and share common things such as eating utensils.

When the virus is transmitted to a person, in almost all circumstances the HIV serology converts to a positive status within 12 weeks. The infection does not produce clinical symptoms for many years in most cases, however.

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In 6 years after seroconversion only 36% will have actually developed AIDS, with its enlarged lymph nodes, body wasting, opportunistic infections, and neoplasms such as Kaposi's sarcoma. It is not known at present whether the remaining 64% of HIV–positive patients will progress to full-blown AIDS, with its 100% fatality rate. It is important to fully understand the distinction between the asymptomatic HIV–positive serology, with its uncertain prognosis, and AIDS itself.

Thoracic surgeons have an obvious exposure to blood from patients during operations, particularly cardiovascular operations. It seems, however, that vascular and cardiac operations are done under controlled conditions whereby the risk of contamination to the surgeon can be minimized. The other members of the team—the anesthetist, perfusionists, nurses, and housekeeping personnel—also are exposed. An overall plan is needed within each operating room and each intensive care unit in every hospital to minimize the exposure to blood for all hospital personnel.

If patients who are to undergo elective operations are screened for HIV, extra precautions may then be taken when caring for the patients whose test results are positive. As some patients require emergency operations (and the HIV test cannot be done quickly), it is not feasible to require testing of all patients before beginning treatment. It is currently estimated that there are more than 1.5 million HIV–positive people in the US. If a double standard of protection is developed, one for known HIV–positive patients and another behavior pattern when treating all other patients, predictably, the greatest risk will come from the patients whose status is unknown. Therefore, the time has come that *all* health care workers must routinely observe *universal precautions* to provide barriers not only to blood but to all body fluids from *all* patients. These universal precautions are listed separately in this report.

Problems With Routine Human Immunodeficiency Virus Screening

Individual screening of patients for HIV is a complex and time-consuming process. The ELISA (enzyme-linked immunosorbent assay) screening test, done on all donated blood, can be completed in a few hours. It has few false negatives, but a substantial number of false positives. This is satisfactory for a unit of donated blood because all positives can be discarded. For a patient who is positive for the ELISA test, however, a confirmatory test such as the Western blot (which has a much lower false positive rate), must be done. A patient with a confirmed positive test needs to be educated as to the meaning of the test, and the test results cannot be allowed to become public knowledge to protect the patient from discrimination within the hospital, school, and workplace. In addition, some jurisdictions have enacted statutes specifically addressing the confidentiality of HIV test results; the surgeon should be aware of any such applicable laws.

Currently, many hospital laboratories perform these screening tests only on specific days of the week in order to run them in economically efficient batches. If hospitalized patients were to be routinely screened before elective operations, the laboratories would have to provide this service in a more timely manner.

There are good reasons to test patients for HIV other than to help the physician take precautions. The presence of HIV infection may alter the expected results of treatment of other health problems. This possibility urgently needs to be proved or refuted. The only way it will be possible to do so in a timely fashion is to record the HIV status of a large number of patients who are being treated for other health problems. The current legal interference in obtaining this information regarding patients undergoing cardiopulmonary bypass is unprecedented. Perhaps laws that prevent discrimination against citizens who are positive for HIV will make testing easier to obtain.

As blood transfusions are definitely implicated in the transmission of HIV, it would seem prudent to establish the status of each patient before each elective procedure such as an open heart operation in which the use of transfusion of blood products is likely. If, sometime after a heart operation, a patient develops AIDS, it is likely he or she will blame the operation and its transfusions when, in fact, a positive serology may have predated the operation.

In this era of reoperation for cardiac disease, there is a special need to know the HIV status of the patient about to undergo another operation. Before the institution of strict screening procedures by blood banks of blood products for transfusion, there was a sizable risk in their use. At the Cedars-Sinai Medical Center in Los Angeles it has been calculated that in the peak year of 1982, the risk of HIV infection was 0.7% per unit of blood or blood product. Patients having heart operations at that time bore a substantial risk, considering that many of them received several units of blood, fresh frozen plasma, or platelets. Using that 0.7% figure, a patient having a heart operation in Los Angeles in 1982, and who received 2 units of blood, 2 units of fresh frozen plasma, and 10 units of platelets (a not infrequent occurrence), carried a 10% chance of HIV seroconversion.

Surgeons should take a leadership role in advising the routine HIV testing of patients before major surgical procedures in which the use of blood may be expected. If routine testing of patients before elective operations is ordered, we may learn about the risks of transmission of HIV and acceleration from a positive HIV status to actual AIDS. A reasonable extension of this logic is to recommend the periodic testing of surgeons. In this way, if large numbers of surgeons are tested, we can more quickly establish the true risk to health care workers that this disease presents.

The Ethics of a Physician Refusing Care to a Patient

A conventional view is that a physician has a right to freely choose whom he or she will accept to treat. If one accepts the premise that the medical profession is dedicated toward service to the sick, some rather powerful ethical forces come into play. A fireman who refuses to fight a fire; a policeman who declines to try to stop a murderer or robber; a lifeguard who believes the waves are too big to attempt a rescue; or a soldier who disobeys orders because he, unlike his commander, thinks the mission too risky undoubtedly would be subjected to disciplinary action. A physician may decline to treat a patient because he or she feels that the requirements for treatment lie outside his or her area of expertise. However, if a physician declines to render treatment because of the patient's inability to pay, personal dislike for the patient, or simply because of fear of the patient's disease, this violates the generally accepted ethical guidelines for the medical profession. Physicians have always borne risks to their own health when treating patients with communicable diseases. Both the American Medical Association and the American College of Physicians have endorsed statements that a physician may not ethically refuse to treat a patient solely because a patient has AIDS or is seropositive. The risks to the physician provided by the AIDS epidemic are likely no greater than those in the past, such as tuberculosis and hepatitis.

Does Cardiopulmonary Bypass Accelerate the Course of Acquired Immunodeficiency Syndrome?

There have been suggestions that surgical procedures and anesthesia, and particularly the use of cardiopulmonary bypass, may temporarily depress the immune system. Additionally, evidence is accumulating that blood transfusions alter the body's immune response. If these statements are true, there may be reason to suspect that any major operation, but particularly heart operations, could be a major factor in accelerating an asymptomatic but positive HIV status into true AIDS. Decisions about whether to advise a patient to have an open heart operation always involve calculating the risk-benefit ratio. Many times the risk factors and benefit factors are "best guesses" rather than definite knowledge of specific numbers. A positive HIV status in a patient introduces further uncertainty into these determinations. In many patients with AIDS, heart operations aimed at prolonging life simply may not be justified. Clearer guidelines will evolve as greater knowledge and understanding of this disease unfold. This knowledge can be gained, however, only if the HIV status of as many patients as possible is known. Our profession, with the cooperation of those groups opposed to testing, has an obligation to obtain the necessary scientific facts to answer these questions.

Universal Blood and Body Fluid Precautions

1. Extraordinary attention should be given to prevent accidental punctures with needles or other sharp instruments, not only to yourself, but also to your fellow workers. By establishing disciplined habits, these events can be minimized so that they are extremely rare. This effective operative behavior does not necessarily prolong operations. Utmost precautions should also be taken when disposing of or cleaning sharp instruments to prevent accidental punctures.
2. Gloves should be worn by all personnel when touching blood or blood-tinged body fluids, mucous membranes, or nonintact skin. Gloves should also be worn when handling blood-stained instruments, sponges, towels, or other objects. Ultrathin gloves probably should not be worn for prolonged operations. Whether to double glove for procedures that are likely to result in torn gloves is a decision for the individual surgeon.
3. Hands and other skin surfaces should be washed thoroughly after any contamination with blood or other body fluids. Hands should be washed after removal of gloves.
4. Gowns with an impervious surface should be worn during any procedure in which the clothing may be soiled with blood, body fluids, secretions, or excretions.
5. When performing the types of operation in which sprays or spurts of blood may be propelled substantial distances (such as cardiac, vascular, orthopedic, dental, and tracheal procedures), all personnel within range should wear not only the customary gowns, gloves, and masks, but also protective eyewear.
6. If the outside of a blood container is visibly contaminated with blood, it should be cleaned with a disinfectant such as sodium hypochlorite.
7. Blood spills should be promptly cleaned up with a disinfectant solution.
8. Articles soiled with blood should be placed in an impervious bag prominently labeled "Blood Precautions" before being sent for disposal or reprocessing.

These universal precautions do not necessarily need to apply to nasal secretions, sputum, sweat, tears, urine, vomitus, or feces unless these contain blood. The risk of transmission of HIV from these fluids is thought to be extremely low. Particularly for blood, however, barrier protection should be used to prevent exposure from *all* patients.

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CORRESPONDENCE

Central Aortopulmonary Shunt Using Gore-Tex: The Modified Davidson Shunt?

To the Editor:

Having trained at The Hospital for Sick Children, London, we were pleased to see the article "The Waterston Shunt: A Commentary" [1], giving proper recognition to the work of David Waterston. Thirty years after the original description of subclavian to pulmonary artery anatomosis by Blalock and Taussig, a modification was introduced using a section of Gore-Tex tube in place of the divided subclavian artery [2]. As the search for the "perfect" shunt goes on we were interested to note the recent description of a modification of the Waterston shunt, using a short section of Gore-Tex to join the ascending aorta to the right pulmonary artery [3].

However, no shunt has proved to be ideal and we were particularly interested in the recent renewed interest in central shunts. Barragry and associates [4] have recently reported good results in 23 neonates using a short segment of polytetrafluoroethylene between the ascending aorta and main pulmonary artery via an anterior approach. In this context we wish to draw attention to the work of a general thoracic surgeon working in the 1950s in a general hospital, Bradford Royal Infirmary in Yorkshire, England. In 1955 James Davidson [5] described a direct anastomosis between the ascending aorta and main pulmonary artery—the first successful central aortopulmonary shunt. In his discussion he attributes the original concept to Blalock and the experimental work done in dogs by Scott and Sabiston and puts his success down to the use of the Potts-Smith clamp. He felt that this shunt may have a place where the Blalock-Taussig anastomosis was technically not possible or in infants with small branch pulmonary arteries.

Surgical tradition dictates that we use the term *modified Blalock-Taussig* for shunts between the subclavian and branch pulmonary artery using Gore-Tex. In keeping with this we would suggest that the term *modified Davidson* be used for the central aorta to main pulmonary artery shunt using Gore-Tex.

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Reply

To the Editor:

I appreciate the opportunity to comment on the letter from J. R. L. Hamilton and D. R. Walker. Certainly recognition should be given to James Davidson for first describing his ingenious approach and technique of an ascending aorta–common pulmonary artery anastomosis to establish a systemic–pulmonary shunt. This is truly a central aortopulmonary shunt, with reference to both the systemic and pulmonary circulations. If the pulmonary artery is used as the primary reference point, aortopulmonary shunts could be classified as (a) central (Davidson), (b) left (Potts), and (c) right (Waterston). Such classification would be consistent and clear as to location and origin. The term *modified Blalock-Taussig* has been accepted as connecting the subclavian artery to the pulmonary system with the aid of a Gore-Tex graft, as pointed out by Hamilton and Walker. Logically, a similar modification using a graft to connect the ascending aorta to the common pulmonary artery should be termed a *modified Davidson* shunt. Extending this concept further, if a graft is used to connect the descending aorta to the left pulmonary artery this should be identified as a *modified Potts* shunt, and a graft between the ascending aorta and right pulmonary artery a *modified Waterston* shunt.

My colleagues and I are indebted to Hamilton and Walker for suggesting this terminology and thank them for bringing this to our attention.

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Reporting the Results of Heart Valve Operations

To the Editor:

We have read with great interest the recent report by Edmunds and colleagues entitled "Guidelines for reporting morbidity and mortality after cardiac valvular operations" [1–3]. We congratulate Edmunds and colleagues on a valiant attempt to standardize the reporting of clinical results of heart valve operations. We should like to make the following comments about the guidelines.

The authors define valve thrombosis as an episode of thromboembolism. We maintain that systemic embolism and valve thrombosis are two events that differ both in nature and in magnitude. Although Edmunds and colleagues concede that valve thrombosis may be listed as a separate subcategory of "thromboembolism," we do not see any advantage to reporting both complications in the same category at all. Whereas systemic embolism often reflects patient variables, we remain convinced that valve thrombosis is very closely related to valve design and materials, and should be listed along with other modes of valve failure such as structural disruption. Nowhere is this clearer than in *The Annals*' own abbreviated guidelines [4], in which structural deterioration and nonstructural dysfunction are defined as a change or abnormality in valve function "causing stenosis or regurgitation," a definition that most certainly describes valve thrombosis.

Edmunds and colleagues recommend that linearized event rates should not be used unless the hazard function for the complication under study "is proved to be constant during the entire time interval considered." We know of no valve-related complication with a hazard function that has been proved to be constant with time. Furthermore, with the possible exception of anticoagulant-related hemorrhage, we can think of no valve-related complication for which this condition is likely to be satisfied. Are Edmunds and colleagues recommending that we do away with linearized rates altogether? If that is the case, we beg to differ. Linearized incidence rates can still be useful in comparing incidences between two series with a similar range of follow-up. We submit that such figures can be compared directly as incidences with confidence intervals without recourse to repeated processing of the raw data and the application of sophisticated statistical analysis (such as the Mantel-Haenzel statistic for actuarial curves). We believe the reporting of linearized incidence rates should continue for all valve-related complications.

Edmunds and colleagues also recommend that if linearized rates are to be reported, they should be "reported with appropriate confidence limits (eg, standard error)." Standard error is not an appropriate confidence limit for valve-related complications. We consider these events to be Poisson parameters for which the appropriate measurement of confidence intervals has been described by Mulder in 1983 [5] and used by ourselves [6] in 1987.

Edmunds and colleagues define nonstructural dysfunction as "valve dysfunction exclusive of thromboembolism and infection diagnosed by reoperation, autopsy, or clinical investigation." It is not clear whether the clause "diagnosed by. . ." refers to the defined dysfunction, its exclusions, or both. We would appreciate clarification of this point. They also recommend "valve-related mortality, including operative deaths and permanent disability" as a useful reporting combination. Disability is *not* mortality. We presume that what is meant by this grouping is the sum of the following events: operative mortality, late valve-related mortality, and permanent disability, but this is ambiguous in the above expression. These would be minor points in most scientific articles, but in an article that aims to promote standardized definitions and reporting methods, correct syntax and clarity are of crucial importance.

With the exception of the above points, we are delighted that the guidelines appear to be in total agreement with our own guidelines published a year ago [7].

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Reply

To the Editor:

The Committee appreciates Dr Nashef and Dr Bain's interest in the guidelines and offers these comments to the points raised in their letter.

Available information indicates that valve thrombosis and thromboembolism are different manifestations of the same pathological process. In one instance the thrombus migrates and in the other it does not. We agree the process is influenced by valve design and materials, but it is also influenced by other factors that are independent of the prosthesis (eg, cardiac output, infection, and anticoagulant drugs). For this reason we included valve thrombosis as a subheading under "thromboembolism." In all likelihood a new means to prevent one manifestation will also prevent the other. However, if the guidelines are followed, reported incidences of valve thrombosis may be added to the complications reported under the heading "structural deterioration" to provide the data that Dr Nashef and Dr Bain desire.

Unfortunately, calculations of linearized rates for various valve-related events are not applicable and frankly misleading if the events occur randomly or at nonconstant rates. Most valve-related events are not constant (with the possible exception of anticoagulant-related bleeding). Event history analysis of retrospective data and calculation of hazard functions indicate the mathematical risk that an event will occur at various time intervals after operation or any other starting point. Hazard diagrams are more difficult to calculate and to compare, but provide more information and more reliable information than do calculations of linearized rates. The Committee feels that it is better to learn and use the more applicable statistics than to persist with the more familiar but misleading linearized rates.

Autopsy, reoperation, and clinical investigation are the only methods available to determine valve dysfunction, thromboembolism, and infection and, therefore, the Committee fails to perceive the ambiguity. From a patient's viewpoint reoperation (without death) and permanent disability are adverse outcomes of prosthetic valve operations. The suggested combinations list different adverse outcomes. The suggested list is not exhaustive, but is designed to emphasize unfavorable outcomes. A prosthetic valve that requires 50% of patients to have reoperation within 1 year or one that causes 50% of patients to suffer permanent strokes would not be popular even if the valve-related mortality rate was low.

The Committee again thanks the large number of individuals who contributed to the development of the published guidelines. We regret any deficiencies, but appreciate the favorable comments that we have received and the widespread acceptance of the document.

L. Henry Edmunds, Jr, MD, Chairman
Richard E. Clark, MD
Lawrence H. Cohn, MD
D. Craig Miller, MD
Richard D. Weisel, MD

Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity
The Society of Thoracic Surgeons and the American Association of Thoracic Surgery

Author Index
Volume 47 (January–June 1989)

KEY TO ABBREVIATIONS USED FOR ARTICLE CLASSIFICATION

* = Original Article
AN = Announcement
CL = Classics in Thoracic Surgery
CR = Case Report
CP = Correspondence
CT = Collective Review
CV = Current Review
ED = Editorial
HW = How to Do It
KR = Key References
PA = Presidential Address
RE = Report
RV = Review of Recent Books

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* = Original Article
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CL = Classics in Thoracic Surgery
CR = Case Report
CP = Correspondence
CT = Collective Review
CV = Current Review
ED = Editorial
HW = How to Do It
KR = Key References
PA = Presidential Address
RE = Report
RV = Review of Recent Books

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- 1988 Meeting, Southern Thoracic Surgical Association 1989;47:72,AN

Annuloplasty
- Mitral valve annuloplasty: The effect of the type on left ventricular function (David, Komeda, & others) 1989;47:524–8*

Antibiotics
- Effect of surgical blood loss and volume replacement on antibiotic pharmacokinetics (Sue, Salazar, & others) 1989;47:357–9*

Anticoagulants
- Anticoagulant therapy in children with prosthetic valves (Rao, Solymar, & others) 1989;47:589–92*

Antioxidants
- Myocardial salvage with Trolox and ascorbic acid for an acute evolving infarction (Mickle, Li, & others) 1989;47:553–7*

Aorta
- Correction of aortico–left ventricular tunnel during the first day of life (Hucin, Horvath, & others) 1989;47:254–6*
- Use of a new stapling instrument for permanent occlusion of the aorta in the surgical procedure for thromboexclusion (Odagiri, Shimazu, & others) 1989;47:466–9,HW

Aorta, ascending
- Combined ascending aorta rupture and left main bronchus disruption from blunt chest trauma (Marzelle, Nottin, & others) 1989;47:769–71,CR
- Treatment of bulboventricular foramen stenosis by ventricle-ascending aorta valved-conduit bypass (Bethea & Reynolds) 1989;47:765–6,CR

Aorta, coarctation of
- Aneurysms after patch graft aortoplasty for coarctation of the aorta: Long-term results of surgical management (Ala-Kulju & Heikkinen) 1989;47:853–6*

Aorta, thoracic
- Malignant fibrous histiocytoma obstructing the thoracic aorta (Guttentag, Lazar, & others) 1989;47:775–7,CR
- New technique for repair of ascending thoracic aortic dissections (Vasseur & Hammond) 1989;47:318–9,HW

Aortic aneurysm
- In situ prosthetic graft replacement for mycotic aneurysm of the aorta (Chan, Crawford, & others) 1989;47:193–203*

Aortic arch
- Extrathoracic and transthoracic management of vascular disease of the aortic arch branches: A 16-year experience (Farina, Sterpetti, & others) 1989;47:580–5*

Aortic root
- Cardioplegia delivery by combined aortic root and coronary sinus perfusion (Kalmbach & Bhayana) 1989;47:316–7,HW
- Composite valve-graft replacement of aortic root using separate Dacron tube for coronary artery reattachment (Coselli & Crawford) 1989;47:558–65*
- Coronary sinus versus aortic root perfusion with blood cardioplegia in elective myocardial revascularization (Fiore, Naunheim, & others) 1989;47:684–8*
- Homograft aortic root replacement to correct infective endocarditis requiring seven open cardiac procedures (Saldanha, Raman, & others) 1989;47:300–1,CR
- A technique for aortic root replacement by an aortic allograft (McGiffin & O'Brien) 1989;47:625–7,HW
- Traumatic aorto–right atrial fistula after blunt chest injury (Chang, Chu, & Lee) 1989;47:778–9,CR

Aortic stenosis
- Management of subaortic stenosis in the univentricular heart (Trusler & Freedom) 1989;47:643–4,ED

Aortic valve
- Allograft aortic valve replacement for bicuspid aortic valves with 180-degree coronary ostia (Hopkins) 1989;47:930–2*
- Improved early results after aortic valve replacement: analysis by surgical time frame (Di Lello, Flemma & others) 1989;47:51–6*
- Viable and nonviable aortic homografts in the subcoronary position: A comparative study (Bodnar, Matsuki, & others) 1989;47:799–805*

Aortocoronary bypass
- Anticipation of bypass surgery: Can it induce silent myocardial ischemia? (Plawes, Charlap, & others) 1989;47:586–8*
- Apparent coagulopathy caused by infusion of shed mediastinal blood and its prevention by washing of the infusate (Griffith, Billman, & others) 1989;47:400–6*
- Coronary artery bypass grafting for unstable angina pectoris: Risk analysis (Naunheim, Fiore, & others) 1989;47:569–74*
- Coronary sinus versus aortic root perfusion with blood cardioplegia in elective myocardial revascularization (Fiore, Naunheim, & others) 1989;47:684–8*
- Disrupted coronary artery caused by angioplasty: Supportive and surgical considerations (Phillips, Kongtahworn, & others) 1989;47:880–3*
- Emergency coronary artery bypass grafting for failed angioplasty: Risk factors and outcome (Naunheim, Fiore, & others) 1989;47:816–23*
- Fifteen-year results of coronary artery bypass for isolated left anterior descending coronary artery disease (Killen, Arnold, & others) 1989;47:595–9*
- Mortality rates and risk factors in coronary bypass surgery (Anderson) 1989;47:489–90,ED
- Postoperative conduction disturbances: A comparison of blood and crystalloid cardioplegia (Gundry, Sequeira, & others) 1989;47:384–90*
- Prediction of post-cardiopulmonary bypass cardiac output (Chung, Magilligan, & others) 1989;47:297–9*
- Right gastroepiploic artery as a coronary bypass graft (Verkkala, Jarvinen, & others) 1989;47:716–9*
- Right gastroepiploic artery: A third arterial conduit for coronary artery bypass (Mills & Everson) 1989;47:706–11*
- Thermal coronary angiography: A method for assessing graft patency and coronary anatomy in coronary bypass surgery (Mohr, Matloff, & others) 1989;47:441–9*

Aortography
- Diagnosis of traumatic thoracic aortic rupture: A 10-year retrospective analysis (Kram, Appel, & others) 1989;47:282–6*

Aortopulmonary septal defect
- Surgical management of aortopulmonary septal defect (Prasad, Valiathan, & others) 1989;47:877–9*

Arrhythmias
- Cryoablation of septal pathways in patients with supraventricular tachyarrhythmias (Lee, Crawford, & others) 1989;47:566–8*
- Mitral valve function after cryoablation of the posterior papillary muscle in the dog (Guiraudon, Guiraudon, & others) 1989;47:872–6*

Arteries, great
- Asymptomatic child a long time after the Mustard operation for transposition of the great arteries (Bink-Boelkens, Bergstra & others) 1989;47:45–50*
- Ten years' experience with the Senning operation for transposition of the great arteries: Physiological results and late follow-up (Bender, Stewart, & others) 1989;47:218–23*

Arteriovenous malformations
- Familial multiple-organ arterial ectasia with massive hemoptysis (Su & Su) 1989;47:461–3,CR

Ascorbic acid
- Myocardial salvage with Trolox and ascorbic acid for an acute evolving infarction (Mickle, Li, & others) 1989;47:553–7*

Asphyxia
- Why is the lower torso protected in traumatic asphyxia? A new hypothesis (Thompson, Illescas, & others) 1989;47:247–9*

Atherosclerosis
- Incidence of atherosclerosis in the internal mammary artery (Sisto & Isola) 1989;47:884–6*

Atrioventricular node
- Cryosurgical ablation of accessory atrioventricular pathways without cardiopulmonary bypass: An epicardial approach for Wolff-Parkinson-White syndrome (Watanabe, Koyanagi, & others) 1989;47:257–64*

Atrioventricular valves
- Annuloplastic reconstruction for common atrioventricular valvular regurgitation in right isomerism (Okita, Miki, & others) 1989;47:302–4,CR
- Late reoperation for systemic atrioventricular valve regurgitation after repair of congenital heart defects (Lamberti, Jensen, & others) 1989;47:517–23*

Atrium
- Direct tricuspid closure versus atrial partitioning in Fontan operation for complex lesions (DeLeon, Ilbawi, & others) 1989;47:761–4*
- Right atrial approach for surgical correction of tetralogy of Fallot (Dietl, Torres, & others) 1989;47:546–52*
- Ten years' experience with the Senning operation for transposition of the great arteries: Physiological results and late follow-up (Bender, Stewart, & others) 1989;47:218–23*
- Traumatic aorto–right atrial fistula after blunt chest injury (Chang, Chu, & Lee) 1989;47:778–9,CR

Auscultatory triangle
- Thoracotomy through the auscultatory triangle (Horowitz, Ancalmo, & Ochsner) 1989;47:782–3,HW

Autoperfusion
- Determinants of homologous blood usage utilizing autologous platelet-rich plasma in cardiac operations (Giordano, Giordano, & others) 1989;47:897–90*
- Eighteen to 37 hours' preservation of major organs using a new autoperfusion multiorgan preparation (Chien, Diana, & others) 1989;47:860–7*

Back, metastatic mass
- Pleuropulmonary actinomycosis associated with a systemic-to-pulmonary artery fistula and contralateral metastatic back mass (Miller, Robertson, & others) 1989;47:305–7,CR

Balloon pump
- Use of an intraaortic balloon pump as a pneumatic ventricular assist device controller (Macrae, Glenville, & others) 1989;47:752–5*

Björk-Shiley prosthesis
- Björk-Shiley strut fracture and disc escape: Literature review and a method of disc retrieval (Hendel) 1989;47:436–40*

Bleeding
- Bleeding and anticoagulation (Copeland) 1989;47:88–95*
- A technique for spot application of fibrin glue during open heart operations (Garcia-Rinaldi, Simmons, & others) 1989;47:59–61,HW

Blood
- Determinants of homologous blood usage utilizing autologous platelet-rich plasma in cardiac operations (Giordano, Giordano, & others) 1989;47:897–90*

Blood flow
- Internal banding for palliation of truncus arteriosus in the neonate (Young, Piancastelli, & others) 1989;47:620–2,HW
- More attempts to monitor quality assurance for myocardial revascularization (Miller) 1989;47:641–2,ED
- Percutaneous cardiopulmonary bypass for the treatment of hypothermic circulatory collapse (Laub, Banaszak, & others) 1989;47:608–11,CR
- Prediction of post-cardiopulmonary bypass cardiac output (Chung, Magilligan, & others) 1989;47:297–9*

Blood loss
- Effect of surgical blood loss and volume replacement on antibiotic pharmacokinetics (Sue, Salazar, & others) 1989;47:357–9*

Blood pressure
- Automated control of postoperative hypertension: A prospective, randomized multicenter study (Cosgrove, Petre, & others) 1989;47:678–83*

Blood transfusion
- Apparent coagulopathy caused by infusion of shed mediastinal blood and its prevention by washing of the infusate (Griffith, Billman, & others) 1989;47:400–6*
- Does transfusion modify the outcome of cancer resections? (Kirschner) 1989;47:336–7,ED
- Effect of perioperative blood transfusion on outcome in patients with surgically resected lung cancer (Moores, Piantadosi, & McKneally) 1989;47:346–51*
- Predonated autologous blood use in elective cardiac surgery (Britton, Eastlund, & others) 1989;47:529–32*

Boerhaave's syndrome
- Spontaneous rupture of the esophagus: A 30-year experience (Pate, Walker, & others) 1989;47:689–92*

Book reviews
- *Brain Injury and Protection During Heart Surgery,* edited by Hilberman (Moreno-Cabral) 1989;47:740,RV
- *Cardiac Arrhythmias: Recent Progress in Investigation and Management,* edited by Iwa & Fontaine (Wright) 1989;47:449,RV
- *Cardiac Surgery. Safeguards and Pitfalls in Operative Technique,* by Khonsari (Hammon) 1989;47:771,RV
- *Cardiac Valve Allografts 1962–1987. Current Concepts on the Use of Aortic and Pulmonary Allografts for Heart Valve Substitutes,* edited by Yankah, Hetzer, & others (del Nido) 1989;47:830,RV
- *Clinical Cancer Monographs, Vol. 1. Cancer of the Oesophagus,* edited by Matthews, Waterhouse, & others (Peters) 1989;47:50,RV
- *Computed Tomography of the Chest: A Teaching File,* by Gale & Karlinsky (Olson) 1989;47:793,RV
- *Gastroesophageal Reflux,* edited by Jamieson & Duranceau (Wilkins) 1989;47:585,RV
- *Guides to Clinical Aspiration Biopsy: Lung, Pleura, and Mediastinum,* by Tao (Shields) 1989;47:61,RV
- *The Heart Surgery Handbook. A Patient's Guide,* by Cohan, Pimm, & Jude (Roe) 1989;47:815,RV
- *Heart Valve Replacement and Future Trends in Cardiac Surgery,* edited by Rabago & Cooley (Jacobson) 1989;47:619,RV
- *International Trends in General Thoracic Surgery. Volume 3. Benign Esophageal Disease,* edited by DeMeester & Matthews (Mansour) 1989;47:230,RV
- *International Trends in General Thoracic Surgery, Volume 4, Esophageal Cancer,* edited by Delarue, Wilkins, & Wong (Mathisen) 1989;47:373,RV
- *Intravascular and Intracardiac Interventional Catheter Therapy. Techniques and Instrumentation,* edited by Bonzel & Serruys (Gardner) 1989;47:913.RV
- *Management of Esophageal Disease,* edited by Skinner & Belsey (Shields) 1989;47:568,RV
- *Manual of Postoperative Management in Adult Cardiac Surgery,* by Moreno-Cabral, Mitchell, and Miller (Karlson) 1989;47:755,RV

Book reviews (cont'd)
- *Progress in Critical Care Medicine: Volume 3. Critical Care Cardiology,* edited by Massion (Swain) 1989;47:883,RV
- *Therapy of Lung Metastases. Proceedings of the Symposium "Die Therapie von Lungen-metastasen im interdisziplinaren Konzept," Heidelberg, June 1986,* edited by Drings & Vogt-Moykopf (Little) 1989;47:56, RV
- *Treatment of End-Stage Coronary Artery Disease,* edited by Walter (Connolly) 1989;47:929,RV

Books received
- *Cardiology 1988,* edited by Roberts 1989;47:463
- *Cardiomyopathies: Clinical Presentation, Differential Diagnosis, and Management. Cardiovascular Clinics, First Edition,* edited by Shaver 1989;47:463
- *Clinics in Chest Medicine, Vol. 9, Number 3, Sep 1988. Pulmonary Effects of AIDS,* edited by White & Stover 1989;47:463
- *Inherited Diseases of the Lung,* by Lieberman 1989;47:463
- *Trauma, Sepsis, and Shock. The Physiological Basis of Therapy,* edited by Clowes 1989;47:463

Brachiocephalic arterial disease
- Extrathoracic and transthoracic management of vascular disease of the aortic arch branches: A 16-year experience (Farina, Sterpetti, & others) 1989;47:580–5*

Bridging
- Bridging to cardiac transplantation (Hill) 1989;47:167–71*
- Circulatory support with a centrifugal pump as a bridge to cardiac transplantation (Bolman, Cox, & others) 1989;47:108–12*
- Implantable electrical left ventricular assist system: Bridge to transplantation and the future (Portner, Oyer, & others) 1989;47:142–50*
- Surgical techniques for the implantation of heterotopic prosthetic ventricles (Ganzel, Gray, & others) 1989;47:113–20*
- SWAT team approach to ventricular assistance (Brugger, Bonandi, & others) 1989;47:136–41*
- Total artificial heart: Survival and complications (Muneretto, Solis, & others) 1989;47:151–7*
- Weaning and bridging (Magovern) 1989;47:102–7*

Bronchogenic carcinoma
- Bronchogenic carcinoma in patients under age 40 (Antkowiak, Regal, & Takita) 1989;47:391–3*

Bronchopleural fistula
- Closure of chronic postpneumonectomy bronchopleural fistula using the transsternal transpericardial approach (Ginsberg, Pearson, & others) 1989;47:231–5*

Bronchoscopy
- Bronchoscopic phototherapy at comparable dose rates: Early results (Pass, Delaney, & others) 1989;47:693–9*
- Endoscopy, mediastinoscopy, and thoracoscopy (McElvein) 1989;47:65–7,KR

Bronchus
- Combined ascending aorta rupture and left main bronchus disruption from blunt chest trauma (Marzelle, Nottin, & others) 1989;47:769–71,CR
- Significance of extramucosal residual tumor at the bronchial resection margin (Kaiser, Flashner, & others) 1989;47:265–9*

Bulboventricular foramen stenosis
- Treatment of bulboventricular foramen stenosis by ventricle–ascending aorta valved-conduit bypass (Bethea & Reynolds) 1989;47:765–6,CR

Cancer
- Bronchial carcinoids: A review of 60 patients (Rea, Binda & others) 1989;47:412–4*
- Bronchogenic carcinoma in patients under age 40 (Antkowiak, Regal, & Takita) 1989;47:391–3*
- Bronchoscopic phototherapy at comparable dose rates: Early results (Pass, Delaney, & others) 1989;47:693–9*
- Carcinoma of the esophagus: A comparison of the results of transhiatal versus transthoracic resection (Hankins, Attar, & others) 1989;47:700–5*
- Does transfusion modify the outcome of cancer resections? (Kirschner) 1989;47:336–7,ED
- Effect of perioperative blood transfusion on outcome in patients with surgically resected lung cancer (Moores, Piantadosi, & McKneally) 1989;47:346–51*
- Large cell carcinoma of the lung: A highly aggressive tumor with dismal prognosis (Downey, Sewell, & Mansour) 1989;47:806–8*
- The malignancy of large cell lung carcinomas (Yesner) 1989;47:796–7,ED
- Mucoepidermoid lung tumors (Heitmiller, Mathisen, & others) 1989;47:394–9*
- Preoperative chemotherapy and irradiation for stage III non-small cell lung cancer (Faber, Kittle, & others) 1989;47:669–77*
- Primary small cell carcinoma of the esophagus (McFadden, Rudnicki, & others) 1989;47:477–80,CT
- Significance of extramucosal residual tumor at the bronchial resection margin (Kaiser, Flashner, & others) 1989;47:265–9*

Cardiac output
- Prediction of post-cardiopulmonary bypass cardiac output (Chung, Magilligan, & others) 1989;47:297–9*

Cardiac tampanade
- Late postoperative cardiac tampanade presenting as dysphagia (Bryan, Weston, & Angelini) 1989;47:922–3,CR

Cardiomyopathy
- Clinical and hemodynamic results after mitral valve replacement in patients with obstructive hypertrophic cardiomyopathy (McIntosh, Greenberg, & others) 1989;47:236–46*

Cardiomyoplasty
- Latissimus dorsi dynamic cardiomyoplasty (Chachques, Grandjean, & Carpentier) 1989;47:600–4*

Cardioplegia
- Angiocatheter coronary artery reperfusion before cardioplegia for evolving myocardial infarction (Nishida, Soltanzadeh, & others) 1989;47:470–1,HW
- Cardioplegia delivery by combined aortic root and coronary sinus perfusion (Kalmbach & Bhayana) 1989;47:316–7,HW
- Coronary sinus versus aortic root perfusion with blood cardioplegia in elective myocardial revascularization (Fiore, Naunheim, & others) 1989;47:684–8*
- Detection of cold hemagglutination in a blood cardioplegia unit before systemic cooling of a patient with unsuspected cold agglutinin disease (Dake, Johnston, & others) 1989;47:914–5,CR
- Effect of cold cardioplegic solution and hypothermia on response to acetylcholine in perfused epicardial coronary artery of pig (Furusho, Araki, & others) 1989;47:287–92*
- Enhanced myocardial protection with adenosine (Bolling, Bies, & others) 1989;47:809–15*
- Modified reperfusate after long-term preservation of the heart (Milliken, Billingsley, & Laks) 1989;47:725–8*
- Myocardial adenine nucleotide metabolism in pediatric patients during hypothermic cardioplegic arrest and normothermic ischemia (Lofland, Abd-Elfattah, & others) 1989;47:663–8*
- Myocardial preservation related to magnesium content of hyperkalemic cardioplegic solutions (Reynolds, Geffin, & others) 1989;47:907–13*

Postoperative conduction disturbances: A comparison of blood and crystalloid cardioplegia (Gundry, Sequeira, & others) 1989;47:384–90*

Cardiothoracic surgery

Choosing cardiothoracic surgical residents (Grillo & Wilcox) 1989;47:333,ED

Cardiovascular surgery

Cardiac transplantation in a private hospital (Harrington) 1989;47:338–9,PA

Case reports

Amiodarone-induced pulmonary mass (Piccione, Faber, & Rosenberg) 1989;47:918–9,CR

Annuloplastic reconstruction for common atrioventricular valvular regurgitation in right isomerism (Okita, Miki, & others) 1989;47:302–4,CR

Combined ascending aorta rupture and left main bronchus disruption from blunt chest trauma (Marzelle, Nottin, & others) 1989;47:769–71,CR

Detection of cold hemagglutination in a blood cardioplegia unit before systemic cooling of a patient with unsuspected cold agglutinin disease (Dake, Johnston, & others) 1989;47:914–5,CR

Entrapment of broken guidewire in the left main coronary artery during percutaneous transluminal coronary angioplasty (Sethi, Ferguson, & others) 1989;47:455–7,CR

Extracorporeal pulsatile biventricular support after cardiac transplantation (Icenogle, Williams, & others) 1989;47:614–6,CR

Familial multiple-organ arterial ectasia with massive hemoptysis (Su & Su) 1989;47:461–3,CR

Gastrotracheal fistula: A late complication after transhiatal esophagectomy (Kron, Johnson, & Morgan) 1989;47:767–8,CR

Homograft aortic root replacement to correct infective endocarditis requiring seven open cardiac procedures (Saldanha, Raman, & others) 1989;47:300–1,CR

Late postoperative cardiac tampanade presenting as dysphagia (Bryan, Weston, & Angelini) 1989;47:922–3,CR

Left subclavian arterioesophageal fistula induced by a foreign body (Mok, Chiu, & Cheung) 1989;47:458–60,CR

Malignant fibrous histiocytoma associated with a Dacron vascular prosthesis (Paterson, Meredith, & Craddock) 1989;47:772–4,CR

Malignant fibrous histiocytoma obstructing the thoracic aorta (Guttentag, Lazar, & others) 1989;47:775–7,CR

Mediastinal involvement by myxoid liposarcoma (McLean, Almassi, & others) 1989;47:920–1,CR

Mitral valve fibroelastoma (Gorton & Soltanzadeh) 1989;47:605–7,CR

Pacing lead fracture after a deceleration injury (Grieco, Scanlon, & Pifarre) 1989;47:453–4,CR

Percutaneous cardiopulmonary bypass for the treatment of hypothermic circulatory collapse (Laub, Banaszak, & others) 1989;47:608–11,CR

Pleuropulmonary actinomycosis associated with a systemic-to-pulmonary artery fistula and contralateral metastatic back mass (Miller, Robertson, & others) 1989;47:305–7,CR

Successful management of aberrant subclavian artery–esophageal fistula in an infant (Guzzetta, Newman, & Ceithaml) 1989;47:308–9,CR

Successful repair of left ventricular rupture after redo mitral valve replacement (Dhillon, Randhawa, & Pett) 1989;47:916–7,CR

Survival of a recipient of renal transplantation after pulmonary phycomycosis (Hsu, Clayman, & Geha) 1989;47:617–9,CR

Systemic-to-pulmonary artery shunt using the internal mammary artery (Longaker, Merrick, & others) 1989;47:464–5,CR

Transpericardial bronchial closure with omentopexy for postpneumonectomy bronchopleural fistula (Saito, Tatsuzawa, & others) 1989;47:312–3,CR

Traumatic aorto–right atrial fistula after blunt chest injury (Chang, Chu, & Lee) 1989;47:778–9,CR

Traumatic laceration of a saphenous vein graft: Successful surgical repair (Harada, Sakakibara, & others) 1989;47:924–5,CR

Traumatic rupture of the pulmonary artery (Collins & Robinson) 1989;47:612–3,CR

Treatment of bulboventricular foramen stenosis by ventricle–ascending aorta valved-conduit bypass (Bethea & Reynolds) 1989;47:765–6,CR

Use of a total wash-out method in an open heart operation (Lee, Chang, & Hsieh) 1989;47:57–8,CR

Vascular sling with tracheomalacia: Surgical management (Conti & Lobe) 1989;47:310–11,CR

Cellulose

Sutureless fixation of long aortocoronary saphenous vein grafts with oxidized regenerated cellulose (Di Lello, Mullen, & others) 1989;47:473–4,HW

Cerebral blood flow

Physiological changes during temporary occlusion of the superior vena cava in cynomolgus monkeys (Masuda, Ogata, & Kikuchi) 1989;47:890–6*

Cerebrospinal fluid (CSF)

Effect of sodium nitroprusside on spinal cord perfusion and paraplegia during aortic cross-clamping (Marini, Grubbs, & others) 1989;47:379–83*

Chemotherapy

Preoperative chemotherapy and irradiation for stage III non-small cell lung cancer (Faber, Kittle, & others) 1989;47:669–77*

Chest

Combined ascending aorta rupture and left main bronchus disruption from blunt chest trauma (Marzelle, Nottin, & others) 1989;47:769–71,CR

New clamp for intraoperative chest tube placement (Stern & Ponn) 1989;47:926,HW

Traumatic aorto–right atrial fistula after blunt chest injury (Chang, Chu, & Lee) 1989;47:778–9,CR

Ventricular aneurysm due to blunt chest injury (Grieco, Montoya, & others) 1989;47:322–9,CT

Why is the lower torso protected in traumatic asphyxia? A new hypothesis (Thompson, Illescas, & others) 1989;47:247–9*

Children and infants

Anticoagulant therapy in children with prosthetic valves (Rao, Solymar, & others) 1989;47:589–92*

Asymptomatic child a long time after the Mustard operation for transposition of the great arteries (Bink-Boelkens, Bergstra & others) 1989;47:45–50*

Extracorporeal membrane oxygenation for postcardiotomy cardiogenic shock in children (Rogers, Trento, & others) 1989;47:903–6*

Incidence of residual defects determining the clinical outcome after correction of tetralogy of Fallot: Postoperative late follow-up (Calza, Panizzon, & others) 1989;47:428–35*

Late reoperation for systemic atrioventricular valve regurgitation after repair of congenital heart defects (Lamberti, Jensen, & others) 1989;47:517–23*

Long-term results in neonates with pulmonary atresia and intact ventricular septum (Coles, Freedom, & others) 1989;47:213–7*

Children and infants (cont'd)
- Mitral valve replacement in the first 5 years of life (Zweng, Bluett, & others) 1989;47:720–4*
- Myocardial adenine nucleotide metabolism in pediatric patients during hypothermic cardioplegic arrest and normothermic ischemia (Lofland, Abd-Elfattah, & others) 1989; 47:663–8*
- Open heart surgery in infancy (Ebert) 1989;47:321,CL
- Repair of large muscular ventricular septal defects in infants employing left ventriculotomy (McDaniel, Gutgesell, & others) 1989;47:593–4*
- Repair of truncus arteriosus in the neonate and young infant (Bove, Beekman, & others) 1989;47:499–506*
- Successful management of aberrant subclavian artery–esophageal fistula in an infant (Guzzetta, Newman, & Ceithaml) 1989;47:308–9;CR
- Ten years' experience with the Senning operation for transposition of the great arteries: Physiological results and late follow-up (Bender, Stewart, & others) 1989;47:218–23*
- True thymic hyperplasia: A clinicopathological study (Ricci, Pescarmona, & others) 1989;47:741–5*
- Vascular sling with tracheomalacia: Surgical management (Conti & Lobe) 1989;47:310–11,CR

Cigarette smoking
- Bronchogenic carcinoma in patients under age 40 (Antkowiak, Regal, & Takita) 1989;47:391–3*

Circulatory support
- Bleeding and anticoagulation (Copeland) 1989;47:88–95*
- Circulatory support with a centrifugal pump as a bridge to cardiac transplantation (Bolman, Cox, & others) 1989; 47:108–12*
- Extracorporeal pulsatile biventricular support after cardiac transplantation (Icenogle, Williams, & others) 1989; 47:614–6,CR
- Implantable electrical left ventricular assist system: Bridge to transplantation and the future (Portner, Oyer, & others) 1989;47:142–50*
- Interim use of the Jarvik-7 artificial heart: Lessons learned at Presbyterian-University Hospital of Pittsburgh (Griffith) 1989;47:158–66*
- Intraoperative management (Hill) 1989;47:82–7*
- Mechanical cardiac assistance (Pennington) 1989;47:792–3;KR
- Other postoperative complications (Pierce) 1989;47:96–101*
- Patient selection (Pennington) 1989;47:77–81*
- SWAT team approach to ventricular assistance (Brugger, Bonandi, & others) 1989;47:136–41*
- Technique and results with a roller pump left and right heart assist device (Rose, Connolly, & others) 1989;47:124–9*
- Total artificial heart: Survival and complications (Muneretto, Solis, & others) 1989;47:151–7*
- Use of an intraaortic balloon pump as a pneumatic ventricular assist device controller (Macrae, Glenville, & others) 1989; 47:752–5*
- Use of the Pierce-Donachy ventricular assist device in patients with cardiogenic shock after cardiac operations (Pennington, McBride, & others) 1989;47:130–5*
- Weaning and bridging (Magovern) 1989;47:102–7*

Clamps
- New clamp for intraoperative chest tube placement (Stern & Ponn) 1989;47:926,HW

Classics in thoracic surgery
- An early approach to the repair of ruptured mitral closure (McGoon) 1989;47:628–9,CL
- Hypothermia: Its possible role in cardiac surgery (Sealy) 1989; 47:788–91,CL
- In the beginning (Hufnagel) 1989;47:475–6,CL
- Open heart surgery in infancy (Ebert) 1989;47:321,CL
- Superior vena cava-pulmonary artery shunt (Glenn) 1989; 47:62–4,CL
- Unterdruck and Überdruck, 1904 (Meyer) 1989;47:933–8,CL

Coagulation
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Herbert Sloan, MD

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THE
ANNALS OF
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*Official Journal of The Society of Thoracic Surgeons
and the Southern Thoracic Surgical Association*

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Surgery of the Airways, Boston, Massachusetts—July 17–18, 1989

This course is sponsored by the General Thoracic Surgical Department of the Massachusetts General Hospital and the Harvard Medical School Department of Continuing Education. The course is accredited for 16 hours in category 1 of the Physician's Recognition Award of the AMA. For information contact Harvard Medical School Department of Continuing Education, PO Box 825, Boston, MA 02117; or telephone (617) 732-1525.

Third Annual Meeting of the European Society for Vascular Surgery, Malmö, Sweden—September 3–5, 1989

A satellite symposium on pharmacological intervention to increase patency in arterial reconstructions will be held in the same location on September 6–7, 1989. For information on both symposia, contact the Congress Organisation Bureau, ESVS 89, c/o ICM AB, Geijersgatan 50, S-216 19 Malmö, Sweden.

Nineteenth World Congress of The International Society for Cardiovascular Surgery, Toronto, Ontario, Canada—September 5–9, 1989

For information on this meeting, contact XIX World Congress, ISCVS Administrative Offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Fourth World Congress of the International Society for Diseases of the Esophagus, Chicago, Illinois—September 6–8, 1989

This meeting is sponsored by the American College of Chest Physicians and Smith Kline & French Laboratories and is accredited for hour-to-hour credit in category 1 of the Physician's Recognition Award of the AMA. For information, contact the American College of Chest Physicians, PO Box 93826, Chicago, IL 60673.

The Third Current Controversies & Techniques in Congenital Heart Surgery, Baltimore, Maryland—September 8–9, 1989

For information on this meeting, contact Terry Slade Young, Current Controversies and Techniques in Congenital Heart Surgery, 11 S Paca St, University Square Bldg, Suite 304, Baltimore, MD 21201.

Twenty-fifth Annual Meeting of The Society of Thoracic Surgeons, Baltimore, Maryland—September 10–13, 1989

For information on this meeting, contact George C. Kaiser, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Thirty-eighth Annual Meeting of The Scandanavian Association for Thoracic and Cardiovascular Surgery and The Scandanavian Society for Extracorporeal Technology, Aarhus, Denmark—September 13–16, 1989

For information on this meeting, contact the Secretary of the Congress Committee SATCVS/SCANSECT, Chr. Mouritzen, MD, Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus-Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

Third Annual Meeting of the European Association for Cardio-Thoracic Surgery, Munich, Federal Republic of Germany—October 9–11, 1989

For information on this meeting, contact Organizing Secretariat, Interplan Convention and Visitor Service, Sophienstrasse 1, D-8000 Munich 2, FRG; or telephone 089 59 44 92 (telex: 523183 iplan d; facsimile: 089 59 16 10).

Sixth World Congress of Bronchoesophagology, Tokyo, Japan—October 15–18, 1989

This meeting is sponsored by the Organizing Committee of the Sixth World Congress of Bronchoesophagology, the Japan Broncho-esophagological Society, and the Foundation for Advancement of International Science under the auspices of the International Bronchoesophagological Society. For information, contact the Secretariat of the Sixth World Congress of Bronchoesophagology, c/o Japan Convention Services, Inc, Press Center Bldg, 2-2-1 Uchisaiwaicho, Chiyoda-ku, Tokyo 100, Japan; or telephone 03-508-1213 (telex: J33104; facsimile: 03-508-0820).

American College of Surgeons, Atlanta, Georgia—October 15–20, 1989

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050.

Sixteenth World Congress on Diseases of the Chest and the Fifty-fifth Annual Scientific Assembly, American College of Chest Physicians, Boston, Massachusetts—October 30–November 3, 1989

This meeting is sponsored by the American College of Chest Physicians and the International Academy of Chest Physicians and Surgeons. For information, contact the American College of Chest Physicians, 911 Busse Highway, Park Ridge, IL 60068; or telephone (312) 698-2200.

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association, Phoenix, Arizona—November 9–11, 1989

For information on this meeting, contact Gordon F. Murray, MD, Southern Thoracic Surgical Association, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Sixty-second Scientific Session of the American Heart Association, New Orleans, Louisiana—November 13–16, 1989

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 750-5300.

Twenty-fifth Anniversary—Open Heart Surgery, Jerusalem, Israel—December 28, 1989–January 1, 1990

For information on this meeting, contact Joseph B. Borman, MD, or the Secretariat, PO Box 32390, Jerusalem 91323, Israel; or telephone 972-2-663171 (telex: 26205 TRGBL IL; facsimile: 972-2-665277).

Nineteenth Annual Meeting of the German Society for Thoracic, Cardiac, and Vascular Surgery, Bad Nauheim, Federal Republic of Germany—February 22–24, 1990

For information on this meeting, contact Hagen D. Schulte, MD, Professor of Surgery, Department of Thoracic and Cardiovascular Surgery, Heinrich-Heine-University, Moorenstrasse 5, D-4000 Dusseldorf, Federal Republic of Germany.

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 130 Madison Avenue, New York, NY. All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words. There is an additional fee of $13.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

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SITUATIONS AVAILABLE

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to 100, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 100A/G

Cardiothoracic surgeon, BC/BE, recent graduate, to join 3-man group for private practice in 500-bed teaching hospital, Great Lakes area, currently active in cardiac procedures. Practice includes open heart, thoracic, and vascular and pacemaker cases. Replies kept confidential. Send CV, list of cases, and references.

Please respond to 101, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 101A/F

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae and names of references.

Please respond to 102, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 102B/I

Faculty position: The Division of Thoracic and Cardiovascular Surgery, Southwestern Medical School of the University of Texas Southwestern Medical Center, is seeking an individual with strong clinical background in adult cardiovascular/thoracic surgery, along with a commitment to education and research, for a position at the assistant professor level. Must be ABTS certified or eligible.

Send complete curriculum vitae to W. Steves Ring, MD, Chairman, Division of Thoracic and Cardiovascular Surgery, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9031. An equal opportunity employer. 121B/G

Cardiovascular and thoracic surgeon: BE/BC wanted to join progressive, established cardiovascular/thoracic surgeon in a 72-doctor multispecialty group in a Big-10 University community of 100,000 with superb cultural advantages. Initial guarantee and fringes with early associateship. Subsequent income based on productivity.

For confidential consideration, please submit curriculum vitae to 103, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 103B/H

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland, OR 97213-2282. 124C/I

Thoracic-vascular surgeon: Board certified or eligible surgeon wanted to join very active noncardiac thoracic vascular practice in small community with referral base of approximately 125,000. Salary leading to full partnership. Advantages of living in a small community in eastern Ohio less than one hour from large desirable metropolitan area. Will also consider applicants primarily interested in vascular surgery. Respond with curriculum vitae.

Please respond to 107, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 107C/F

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV.

Please respond to 105, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 105C/H

Cardiothoracic surgeon to join established group in northwest Indiana (very near Chicago). Excellent salary. Please respond with curriculum vitae.

Please respond to 104, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 104C/H

First Assistant, Cardiovascular Surgery: Excellent opportunity to join a dynamic 200-physician multispecialty clinic, located in northeastern Pennsylvania, in a challenging position as a Physician's Assistant. Outstanding noncontributory benefits and competitive salary.

Please send resume to Guthrie Clinic, Guthrie Square, Sayre, PA 18840; or telephone (717) 888-5858. 126D/F

Excellent professional opportunity for cardiothoracic surgeon to join director of new adult cardiac and thoracic surgery program in California wine country. Beautiful semirural geographical surroundings, easy access to San Francisco, desirable area for family. Send curriculum vitae and references—new graduate preferred.

Please respond to 110, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 110D/F

Cardiothoracic surgeon: BE/BC, wanted to join established 3-man practice in southern California. Very busy team doing 1,000 cases/yr. Excellent location and benefits. Practice includes all aspects of adult cardiac, thoracic, and vascular surgery. Please respond with curriculum vitae.

Please respond to 111, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 111D/F

Cardiothoracic surgeon wanted for busy, expanding Southeastern private group in regional medical center with university affiliation. Practice includes most aspects of adult and pediatric cardiac and thoracic surgery. Surgeon must be board eligible or certified with contemporary training. Excellent opportunity for suitable applicant.

Please respond to 112, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 112D/G

Cardiovascular/thoracic surgeon for expanding 2-man practice in northwest Florida. Primarily adult cardiac surgery, doing 350–400 cases per year. Please respond with curriculum vitae and references.

Please respond to 137, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 137E/G

Cardiothoracic surgeon, BE/BC, to join established 2-man private practice involved with adult cardiac, thoracic, and vascular surgery in major Midwest community. Salary leading to partnership. Please send CV, clinical experience, and references.

Please respond to 143, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 143E/G

Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits.

Please respond with curriculum vitae to 144, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 144E/D

Cardiothoracic surgeon needed to join established 2-man group in practice of adult cardiac, pulmonary, and vascular surgery. Must be board certified or eligible and graduate from a US medical school.

Please respond to R. W. Ruess, MD, 1834 Broadway, Cape Girardeau, MO 63701. 149E/G

Cardiothoracic surgeon/BC/BE: to establish a cardiothoracic surgery practice in 29-doctor multispecialty group practice. Local 579-bed hospital has received C.O.N. for cardiac surgery. Competitive salary and incentive plus benefit package. Located in Central Florida, lake country.

Please respond to 150, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 150E/G

Cardiovascular surgeon, board certified or eligible, needed for busy, private established practice. Primarily open heart surgery with some peripheral vascular and thoracic surgery. Competitive salary and benefits.

Please send CV and cover letter to 151, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 151FG

Recruiting thoracic/vascular surgeon, VA Medical Center, Clarksburg, West Virginia. Affiliated with West Virginia University. Full surgical residency rotation. Dual appointment.

Respond to Gordon Murray, MD, Professor and Chairman, Department of Surgery, West Virginia University Medical Center, Morgantown, WV 26505; or telephone (304) 293-4869. Equal opportunity employers. 146FG

Cardiothoracic surgeon: Board certified or eligible is sought to join an academic practice in the Midwest. Opportunity to become active and contribute to a growing cardiothoracic transplantation program. Excellent research opportunities available.

Direct curriculum vitae or inquiries to J. Terrance Davis, MD, Medical College of Ohio, C.S. #10008, Toledo, OH 43699. An equal opportunity employer. 153F/I

Cardiothoracic surgeon wanted to join a 2-man group located in an excellent growing community on the southeast coast of Florida. Practice mainly adult cardiac. BC/BE candidate with access to Florida license. Send CV.

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Please respond to 155, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 155FG

Cardiovascular and thoracic surgeon, BE/BC, wanted to join a busy private practice in Pittsburgh, PA. Please respond with curriculum vitae and details of experience.

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Academic appointment: Ontario—Queen's University, Department of Surgery, geographic full-time position in cardiothoracic surgery. Applicants should be licensed to practice in Ontario and be Fellows of the Royal College of Physicians and Surgeons of Canada, with Specialist certification in cardiovascular and thoracic surgery. The successful candidate will be expected to teach at undergraduate and postgraduate levels and engage in research. He/she will be expected to share emergency on-call duties including occasional coverage of general thoracic surgery. Salary, ceiling, and academic rank will be by negotiation according to qualifications and experience. In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents of Canada. The closing date for application is July 31, 1989. Candidates of both sexes will be given equal consideration.

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Cardiovascular and thoracic surgeon, 40, wishes to relocate, preferably in the Southeast. American university trained, ABS, ABTS, FACS. Private practice experience in adult cardiac, thoracic, and peripheral vascular surgery. Willing to initiate new program. Curriculum vitae and references upon request.

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Cardiovascular and thoracic surgeon wishes to relocate. University trained with ABTS certification. Ten years' experience with extensive cardiac, thoracic, and peripheral vascular surgery. Would be interested in starting new program or association with group. Curriculum vitae and references available upon request.

Please respond to 117, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 117C/H

Cardiovascular and thoracic surgeon, 37, ABS, ABTS, personable, strong technical skills and patient care, interested in joining group or starting new program.

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Cardiovascular and thoracic surgeon wishes to relocate. ABS, ABTS with 10 years experience in adult cardiac, thoracic, and peripheral vascular surgery. All areas considered. Willing to initiate or help initiate new program.

Please respond to 136, The Annals of Thoracic Surgery, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010. 136E/H

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Please contact Prof Gideon Uretzky, Joseph Lunenfeld Cardiac Surgery Research Center, Hadassah University Hospital, POB 12000, Jerusalem 91120, Israel; or telephone 446790. 127D/F

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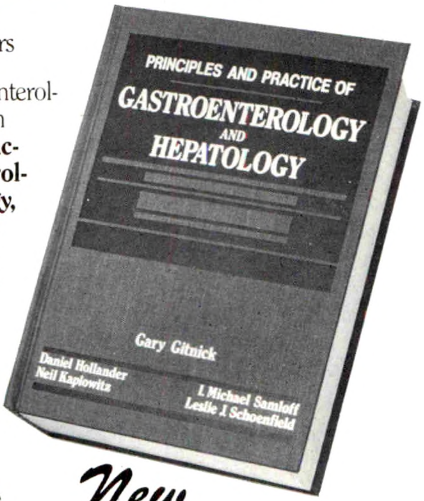

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